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Essex CM19 5AW (GB). **PORTER, Roderick, Alan**
[GB/GB]; GlaxoSmithKline, New Frontiers Science Park
South, Third Avenue, Harlow, Essex CM19 5AW (GB).

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(74) Agent: **HOCKLEY, Siân, Catherine**; GlaxoSmithKline,
Corporate Intellectual Property CN925.1, 980 Great West
Road, Brentford, Middlesex TW8 9GS (GB).

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(71) Applicant (for all designated States except US):
SMITHKLINE BEECHAM P.L.C. [GB/GB]; 980
Great West Road, Brentford, Middlesex TW8 9GS (GB).

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(72) Inventors; and
(75) Inventors/Applicants (for US only): **CHAN, Wai, Ngor**
[GB/GB]; GlaxoSmithKline, New Frontiers Science Park
South, Third Avenue, Harlow, Essex, CM19 5AW (GB).
JOHNS, Amanda [GB/GB]; GlaxoSmithKline, New
Frontiers Science Park South, Third Avenue, Harlow,
Essex CM19 5AW (GB). **JOHNSON, Christopher, Norbert**
[GB/GB]; GlaxoSmithKline, New Frontiers Science
Park South, Third Avenue, Harlow, Essex CM19 5AW
(GB). **NOVELLI, Riccardo** [IT/GB]; GlaxoSmithKline,
New Frontiers Science Park South, Third Avenue, Harlow,

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(54) Title: COMPOUNDS

(57) Abstract: This invention relates to <i>N</i>-aryloyl cyclic amine derivatives and their use as pharmaceuticals, specifically as orexin receptor antagonists.

COMPOUNDS

This invention relates to *N*-acyl cyclic amine derivatives and their use as pharmaceuticals.

Many medically significant biological processes are mediated by proteins participating in 5 signal transduction pathways that involve G-proteins and/or second messengers.

Polypeptides and polynucleotides encoding the human 7-transmembrane G-protein coupled neuropeptide receptor, orexin-1 (HFGAN72), have been identified and are disclosed in EP-A-875565, EP-A-875566 and WO 96/34877. Polypeptides and polynucleotides encoding a second human orexin receptor, orexin-2 (HFGANP), have been identified and are disclosed in 10 EP-A-893498.

Polypeptides and polynucleotides encoding polypeptides which are ligands for the orexin-1 receptor, e.g. orexin-A (Lig72A) are disclosed in EP-A-849361.

Orexin receptors are found in the mammalian host and may be responsible for many biological functions, including pathologies including, but not limited to, depression; anxiety; 15 addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delerium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Gilles de la Tourett's syndrome; disturbed biological and circadian 20 rhythms; feeding disorders, such as anorexia, bulimia, cachexia, and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's disease; Cushing's syndrome / disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumor / adenoma; hypothalamic diseases; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; pituitary growth hormone; 25 adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth 30 hormone deficiency; dwarfism; gigantism; acromegaly; and sleep disturbances associated with such diseases as neurological disorders, neuropathic pain and restless leg syndrome, heart and lung diseases; acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischaemic or haemorrhagic stroke; 35 subarachnoid haemorrhage; head injury such as sub-arachnoid haemorrhage associated with traumatic head injury; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain, such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection, e.g. HIV, post-polio syndrome, and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke 40 pain; post-operative pain; neuralgia; nausea and vomiting; conditions associated with visceral pain including irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegenerative disorders,

which includes nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration, epilepsy, and seizure disorders.

Experiments have shown that central administration of the ligand orexin-A (described in more detail below) stimulated food intake in freely-feeding rats during a 4 hour time period. This increase was approximately four-fold over control rats receiving vehicle. These data suggest that orexin-A may be an endogenous regulator of appetite. Therefore, antagonists of its receptor may be useful in the treatment of obesity and diabetes, see *Cell*, 1998, **92**, 573-585.

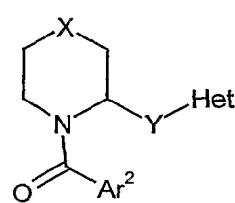
There is a significant incidence of obesity in westernised societies. According to WHO definitions a mean of 35% of subjects in 39 studies were overweight and a further 22% clinically obese. It has been estimated that 5.7% of all healthcare costs in the USA are a consequence of obesity. About 85% of Type 2 diabetics are obese, and diet and exercise are of value in all diabetics. The incidence of diagnosed diabetes in westernised countries is typically 5% and there are estimated to be an equal number undiagnosed. The incidence of both diseases is rising, demonstrating the inadequacy of current treatments which may be either ineffective or have toxicity risks including cardiovascular effects. Treatment of diabetes with sulphonylureas or insulin can cause hypoglycaemia, whilst metformin causes GI side-effects. No drug treatment for Type 2 diabetes has been shown to reduce the long-term complications of the disease. Insulin sensitizers will be useful for many diabetics, however they do not have an anti-obesity effect.

Rat sleep/EEG studies have also shown that central administration of orexin-A, an agonist of the orexin receptors, causes a dose-related increase in arousal, largely at the expense of a reduction in paradoxical sleep and slow wave sleep 2, when administered at the onset of the normal sleep period. Therefore antagonists of its receptor may be useful in the treatment of sleep disorders including insomnia.

The present invention provides *N*-aryloyl cyclic amine derivatives which are non-peptide antagonists of human orexin receptors, in particular orexin-1 receptors. In particular, these compounds are of potential use in the treatment of obesity, including obesity observed in Type 2 (non-insulin-dependent) diabetes patients, and/or sleep disorders. Additionally these compounds may be of use in the treatment of stroke, particularly ischemic or haemorrhagic stroke, and/or blocking the emetic response i.e. the compounds are useful in the treatment of nausea and vomiting.

International Patent Applications WO99/09024, WO99/58533, WO00/47577 and WO00/47580 disclose phenyl urea derivatives and WO00/47576 discloses quinolinyl cinnamide derivatives as orexin receptor antagonists.

According to the invention there is provided a compound of formula (I):



(I)

wherein:

X represents a bond, oxygen, NR³ or a group (CH₂)_n, wherein n represents 1, 2 or 3,

Y represents CH₂, CO, CHO_H, or -CH₂CH(OH)-;

Het is an optionally substituted 5- or 6- membered monocyclic heteroaryl group containing up to 4 heteroatoms selected from N, O and S, substituted by R²;

5 Ar² represents an optionally substituted phenyl or a 5- or 6-membered heteroaryl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heteroaryl group is substituted by R¹ and further optional substituents; or Ar² represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic group containing up to 3 heteroatoms selected from N, O and S;

10 R¹ represents hydrogen, an optionally substituted(C₁₋₄)alkoxy, halo, cyano, optionally substituted(C₁₋₆)alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S;

R² is an optionally substituted aryl or an optionally substituted mono or bicyclic heteroaryl group containing up to 3 heteroatoms selected from N, O and S;

15 R³ is selected from hydrogen or (C₁₋₄)alkyl; or a pharmaceutically acceptable salt thereof.

A further aspect of the invention is the compound (RS)-1-dibenzofuran-4-yl-1-{2-[5-(3-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanone or a pharmaceutically acceptable salt thereof.

20 Preferably where Ar² represents phenyl or a 5- or 6-membered heteroaryl group containing up to 3 heteroatoms selected from N, O and S, the R¹ group is situated adjacent to the point of attachment to the amide carbonyl.

Het may have up to 5, preferably 1, 2 or 3 optional substituents.

25 When Het is an optionally substituted 5- or 6- membered monocyclic heteroaryl group containing up to 4 heteroatoms selected from N, O and S, it may be oxazolyl, imidazolyl, thiazolyl, thiadiazolyl, oxadiazolyl, triazolyl, pyrazolyl, furanyl, tetrazolyl, pyrimidinyl, pyrazinyl, pyridazinyl or pyridinyl. Additionally Het may be isoxazolyl, isothiazolyl and triazinyl.

Preferred examples for Het are oxazolyl, imidazolyl, thiazolyl, triazolyl, oxadiazolyl and pyrazolyl. Additional preferred examples are furanyl and tetrazolyl.

30 When Ar² is a 5- or 6-membered heteroaryl group containing up to 3 heteroatoms selected from N, O and S, it may be furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, triazinyl, pyridazinyl, pyridinyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl, or pyrazolyl.

35 Alternatively, examples of Ar² are thiazolyl, pyrazolyl, triazolyl, pyridazinyl, oxazolyl, pyridinyl, pyrimidinyl, isoxazolyl and thienyl.

More specifically, examples of Ar² are thiazolyl, pyrazolyl, triazolyl, pyridazinyl, oxazolyl, pyridinyl, pyrimidinyl, and thienyl.

40 When R¹ is an optionally substituted 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S, it may be furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, triazolyl, triazinyl, pyridazinyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl or pyrazolyl. Alternatively R¹ can be piperidinyl, morpholinyl, thiomorpholinyl and piperazinyl. Additionally R¹ can be tetrazolyl.

Preferably R¹ is an optionally substituted 5- or 6-membered heteroaryl group containing up to 3 heteroatoms selected from N, O and S.

Examples of where Ar^2 represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic include naphthyl, quinolinyl, naphthyridinyl, benzofuranyl, benzimidazolyl, quinoxaliny1 or quinazolinyl. Additionally Ar^2 can be benzothienyl, benzotriazolyl, benzoxazolyl or indazolyl. Furthermore Ar^2 can be isoquinolinyl.

5 When R^2 is a mono or bicyclic heteroaryl group containing up to 3 heteroatoms selected from N, O and S, it can be, for example, benzofuranyl, pyrimidinyl, pyridinyl, pyridazinyl or furanyl.

Preferably Ar^2 represents optionally substituted phenyl, pyridinyl, thiazolyl, pyrazolyl, pyridazinyl, thienyl, benzofuranyl, naphthyl or triazolyl.

10 Alternatively Ar^2 represents optionally substituted phenyl, pyridinyl, thiazolyl, pyrazolyl, pyridazinyl, thienyl, benzofuranyl, naphthyl or 1,2,3-triazolyl.

X is preferably a bond, oxygen, or $(\text{CH}_2)_n$ wherein n is 1 or 2.

Y is preferably CH_2 .

15 Alternatively R^1 represents hydrogen, an optionally substituted(C_{1-4})alkoxy, halo, optionally substituted(C_{1-6})alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heteroaryl group containing up to 3 heteroatoms selected from N, O and S

Furthermore R^1 can represent an optionally substituted(C_{1-4})alkoxy, halo, optionally substituted(C_{1-6})alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heteroaryl group containing up to 3 heteroatoms selected from N, O and S

20 Preferably R^1 is selected from an optionally substituted phenyl, pyridinyl, pyrazolyl, pyrimidazinyl, or oxadiazolyl group.

Preferably R^2 is attached to the atom in the monocyclic heteroaryl ring one removed from point of attachment of Het to the linker as shown in compound (I) of scheme 2a.

25 When used herein the term amide carbonyl means the $-\text{C}(\text{O})\text{N}$ bond wherein the N forms part of the cyclic amide ring

Even more preferably R^1 represents an optionally substituted phenyl, or oxadiazolyl group.

Preferably R^2 is an optionally substituted phenyl.

More preferably Het is oxadiazolyl, oxazolyl, imidazolyl, furanyl, thiazolyl or triazolyl, 30 even more preferably Het is oxadiazolyl, oxazolyl, imidazolyl or furanyl.

Optional substituents for the groups Het, Ar^2 , R^1 and R^2 include halogen, hydroxy, oxo, cyano, nitro, (C_{1-4})alkyl, (C_{1-4})alkoxy, hydroxy(C_{1-4})alkyl, hydroxy(C_{1-4})alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, aryl(C_{1-4})alkoxy, (C_{1-4})alkylthio, hydroxy(C_{1-4})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{3-6})cycloalkyl(C_{1-4})alkoxy, (C_{1-4})alkanoyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylsulfonyl, (C_{1-4})alkylsulfonyloxy, (C_{1-4})alkylsulfonyl(C_{1-4})alkyl, (C_{1-4})alkylsulfonamido, (C_{1-4})alkylamido, (C_{1-4})alkylsulfonamido(C_{1-4})alkyl, (C_{1-4})alkylamido(C_{1-4})alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamido(C_{1-4})alkyl, arylcarboxamido(C_{1-4})alkyl, aroyl, aroyl(C_{1-4})alkyl, or aryl(C_{1-4})alkanoyl group; a group $\text{R}^a\text{R}^b\text{N}-$,

40 $\text{R}^a\text{OCO}(\text{CH}_2)_r$, $\text{R}^a\text{CON}(\text{R}^a)(\text{CH}_2)_r$, $\text{R}^a\text{R}^b\text{NCO}(\text{CH}_2)_r$, $\text{R}^a\text{R}^b\text{NSO}_2(\text{CH}_2)_r$ or $\text{R}^a\text{SO}_2\text{NR}^b(\text{CH}_2)_r$ where each of R^a and R^b independently represents a hydrogen atom or a (C_{1-4})alkyl group or where appropriate R^aR^b forms part of a (C_{3-6})azacycloalkane or (C_{3-6})(2-oxo)azacycloalkane ring and r

represents zero or an integer from 1 to 4. Additional substituents are (C₁₋₄)acyl, aryl, aryl(C₁₋₄)alkyl, (C₁₋₄)alkylamino(C₁₋₄)alkyl, R^aR^bN(CH₂)_n-, R^aR^bN(CH₂)_nO-, wherein n represents an integer from 1 to 4. Additionally when the substituent is R^aR^bN(CH₂)_n- or R^aR^bN(CH₂)_nO-, R^a with at least one CH₂ of the (CH₂)_n portion of the group form a (C₃₋₆)azacycloalkane and R^b 5 represents hydrogen, a (C₁₋₄)alkyl group or with the nitrogen to which it is attached forms a second (C₃₋₆)azacycloalkane fused to the first (C₃₋₆)azacycloalkane.

Preferred optional substituents for Ar² are halogen, cyano, (C₁₋₄)alkyl, hydroxy(C₁₋₄)alkyl, (C₁₋₄)alkoxy(C₁₋₄)alkyl, R^aR^bN(CH₂)_n, or R^aR^bN. Additionally preferred optional substituents are (C₁₋₄)alkoxy, phenyl or nitro.

10 Preferred optional substituents for Het are halogen, cyano, or (C₁₋₄)alkanoyl. Further optional substituents are hydroxy(C₁₋₄)alkyl, (C₁₋₄)alkyl, or CF₃.

Preferred optional substituents for R¹ are halogen, (C₁₋₄)alkoxy(C₁₋₄)alkyl, R^aR^bN, R^aR^bN(CH₂)_n and R^aR^bN(CH₂)_nO. Additional optional substituents are (C₁₋₄)alkoxy, (C₁₋₄)alkanoyl or (C₁₋₄)alkyl.

15 Preferred optional substituents for R² are cyano, (C₁₋₄)alkyl, (C₁₋₄)alkoxy and halogen.

In addition Het may be optionally substituted by a phenyl ring optionally substituted by a halogen, cyano, C₁₋₄alkyl, C₁₋₄alkanoyl or C₁₋₄alkylsulfonyl group; or by a 5- or 6-membered heterocyclic ring, such as a furanyl, pyridinyl, oxazolyl and pyrimidinyl. Additionally Het may be optionally substituted by a phenyl ring optionally substituted by (C₁₋₄)alkoxy.

20 Preferred optional substituents for Ar² include halogen, cyano, and (C₁₋₄)alkyl.

In the groups Het and Ar², substituents positioned *ortho* to one another may be linked to form a ring.

Illustrative compounds of formula (I) can be selected from:

1	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-methanone;
2	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-2H-[1,2,3]triazol-4-yl]-1-[2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-methanone;
3	(RS)-1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-methanone
4	(RS)-1-Naphthalen-1-yl-1-[2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-methanone
5	(RS)-1-[2-(4-Fluoro-phenyl)-5-methyl-2H-pyrazol-3-yl]-1-[2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-methanone
6	(RS)-1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-[2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-methanone
7	(RS)-1-[4-(4-Fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-1-[2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-methanone
8	(RS)-1-[4-(4-Fluoro-phenyl)-1H-pyrazol-3-yl]-1-[2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-methanone
9	(RS)-1-[2-[5-(3-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
10	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-[5-(3-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl]-methanone
11	(RS)-1-[2-[5-(3-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

12	(RS)-1-{2-[5-(3-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
13	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(5-pyridin-2-yl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-methanone
14	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[5-(4-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanone
15	(RS)-1-{2-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
16	(RS)-1-{2-[5-(2-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
17	(RS)-1-{2-[5-(2-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
18	(RS)-1-{2-[5-(2,3-Dichloro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
19	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[5-(2-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanone
20	(RS)-1-[2-(5-Benzofuran-4-yl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
21	(RS)-1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-{2-[5-(2-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanone
22	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-2H-[1,2,3]triazol-4-yl]-1-{2-[5-(2-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanone
23	(RS)-1-{2-[5-(2-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-naphthalen-1-yl-methanone
24	(RS)-1-{2-[5-(2,3-Difluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
25	(RS)-1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-[2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-methanone
26	(RS)-1-{2-[5-(2,5-Difluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
27	(RS)-1-{2-[5-(2,5-Difluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
28	(RS)-1-{2-[5-(2,5-Difluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
29	(RS)-1-{2-[5-(3,5-Difluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
30	(RS)-1-{2-[5-(3,5-Difluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
31	(RS)-1-{2-[5-(3,5-Difluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
32	(RS)-1-{2-[5-(3,5-Difluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
33	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[5-(6-methyl-pyridin-2-yl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanone
34	(RS)-1-[4-(4-Fluoro-phenyl)-1H-pyrazol-3-yl]-1-{2-[5-(6-methyl-pyridin-2-yl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanone
35	(RS)-1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-{2-[5-(6-methyl-pyridin-2-yl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanone
36	(RS)-1-{2-[5-(3-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
37	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(5-furan-2-yl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-methanone
38	(RS)-1-[4-(4-Fluoro-phenyl)-1H-pyrazol-3-yl]-1-[2-(5-furan-2-yl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-methanone
39	(RS)-1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-[2-(5-furan-2-yl-

	[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl]-methanone
40	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-2H-[1,2,3]triazol-4-yl]-1-[2-(5-furan-2-yl-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl]-methanone
41	(RS)-1-{2-[5-(3-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
42	(RS)-1-[5-(3-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[5-(3-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanone
43	(RS)-1-[5-(2-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[5-(3-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanone
44	(RS)-1-[5-(4-Fluoro-phenyl)-thiazol-4-yl]-1-[2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-methanone
45	(RS)-1-[5-(3-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-methanone
46	(RS)-1-[5-(2-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-methanone
47	(RS)-1-[5-(3-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[5-(6-methyl-pyridin-2-yl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanone
48	(RS)-1-[5-(2-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[5-(6-methyl-pyridin-2-yl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanone
49	(RS)-1-{2-[5-(2,3-Difluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
50	(RS)-1-{2-[5-(2,3-Difluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
51	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-pyrrolidin-1-yl]-methanone
52	(RS)-1-[5-(3-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-pyrrolidin-1-yl]-methanone
53	(RS)-1-[5-(2-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-pyrrolidin-1-yl]-methanone
54	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[4-(4-fluoro-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl}-methanone
55	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[4-(2-methoxy-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl}-methanone
56	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[4-(3-fluoro-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl}-methanone
57	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[4-(2-fluoro-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl}-methanone
58	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(5-methyl-4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone
59	(RS)-2-(5-(4-Fluorophenyl)-furan-2-ylmethyl)-1-((5-(4-fluorophenyl)-2-methyl-thiazol-4-yl)carbonyl-piperidine
60	(RS)-1-[2-(4-Fluoro-phenyl)-5-methyl-2H-pyrazol-3-yl]-1-[2-(4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone
61	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-2H-[1,2,3]triazol-4-yl]-1-[2-(4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone
62	(RS)-1-Naphthalen-1-yl-1-[2-(4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone
63	(RS)-1-(5-Bromo-2-methoxy-phenyl)-1-[2-(4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone
64	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(5-phenyl-1H-imidazol-2-ylmethyl)-piperidin-1-yl]-methanone
65	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-1-yl}-methanone
66	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[3-(5-phenyl-[1,3,4]oxadiazol-2-

	ylmethyl)-morpholin-4-yl]-methanone
67	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[3-(4-phenyl-oxazol-2-ylmethyl)-morpholin-4-yl]-methanone
68	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[3-(4-phenyl-1H-imidazol-2-ylmethyl)-morpholin-4-yl]-methanone
69	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-[5-(4-fluoro-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl]-methanone
70	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone
71	(RS)-1-[2-[5-(4-Fluoro-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl]-1-naphthalen-1-yl-methanone
72	(RS)-1-(3,5-Dimethoxy-phenyl)-1-[2-[5-(4-fluoro-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl]-methanone
73	(RS)-1-[2-(4-Fluoro-phenyl)-5-methyl-2H-pyrazol-3-yl]-1-[2-[5-(4-fluoro-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl]-methanone
74	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-2H-[1,2,3]triazol-4-yl]-1-[2-[5-(4-fluoro-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl]-methanone
75	(RS)-1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-[2-[5-(4-fluoro-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl]-methanone
76	(RS)-1-[2-[5-(4-Fluoro-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
77	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(5-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone
78	(RS)-1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-1-[2-(5-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone
79	(RS)-1-(2-Iodo-phenyl)-1-[2-(5-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone
181	(RS)-1-[2-[5-(2,3-Difluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-2H-[1,2,3]triazol-4-yl]-methanone

and pharmaceutically acceptable salts thereof.

Additional compounds of formula (I) can be selected from:

80	1-[(S)-2-[5-(4-Fluoro-phenyl)-1H-imidazol-2-ylmethyl]-pyrrolidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
81	1-[(S)-2-[5-(4-Fluoro-phenyl)-1H-imidazol-2-ylmethyl]-pyrrolidin-1-yl]-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
82	1-[(S)-2-[5-(4-Fluoro-phenyl)-1H-imidazol-2-ylmethyl]-pyrrolidin-1-yl]-1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
83	(RS)-1-[2-[5-(4-Fluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
84	(RS)-1-[2-[5-(4-Fluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
85	(RS)-1-[2-[5-(4-Fluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
86	(RS)-1-[2-[5-(4-Fluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-1-(2-methoxy-pyridin-3-yl)-methanone
87	(RS)-1-[2-[5-(4-Fluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-1-isoquinolin-3-yl-methanone
88	(RS)-1-[2-[5-(4-Fluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-1-[1,8]naphthyridin-2-yl-methanone
89	(RS)-1-[1-(2-Dimethylamino-ethyl)-4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-1-[2-[4-(4-fluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-methanone
90	(RS)-1-[5-(4-Fluoro-phenyl)-2-hydroxymethyl-thiazol-4-yl]-1-[2-[5-(4-fluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-methanone
91	(RS)-1-[2-[4-(4-Fluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-2H-[1,2,3]triazol-4-yl]-methanone

92	(RS)-1-[2-[4-(4-Fluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
93	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-[5-(2-methoxyphenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-methanone
94	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-[5-(2-fluorophenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-methanone
95	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-[5-(2-bromophenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-methanone
96	(RS)-2-[2-(1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl)-piperidin-2-ylmethyl]-3H-imidazol-4-yl]-benzonitrile
97	(RS)-1-[2-[4-Bromo-5-(4-fluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
98	(RS)-5-(4-Fluoro-phenyl)-2-(1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl)-piperidin-2-ylmethyl)-3H-imidazole-4-carbonitrile
102	(RS)-1-(2-Ethoxy-phenyl)-1-[2-(4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone
103	(RS)-1-[5-(4-Fluoro-phenyl)-2-hydroxymethyl-thiazol-4-yl]-1-[2-(4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone
104	(RS)-1-[5-(4-Fluoro-phenyl)-2-hydroxymethyl-thiazol-4-yl]-1-[2-(5-phenyl-1H-imidazol-2-ylmethyl)-piperidin-1-yl]-methanone
105	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-[5-(4-fluoro-phenyl)-4H-[1,2,4]triazol-3-ylmethyl]-piperidin-1-yl]-methanone
106	(RS)-1-[2-[5-(4-Fluoro-phenyl)-4H-[1,2,4]triazol-3-ylmethyl]-piperidin-1-yl]-1-isoquinolin-3-yl-methanone
107	(RS)-1-[2-[3-(3-Dimethylamino-propoxy)-phenyl]-thiophen-3-yl]-1-[2-[4-(4-fluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-methanone
108	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-[5-(3-methoxy-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-methanone
109	(RS)-1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-[2-[5-(3-methoxy-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-methanone
110	(RS)-1-[2-[5-(3-Chloro-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
111	(RS)-1-[2-[5-(3-Chloro-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanone
112	(RS)-3-[2-(1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl)-piperidin-2-ylmethyl]-3H-imidazol-4-yl]-benzonitrile
113	(RS)-3-[2-(1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl)-piperidin-2-ylmethyl]-3H-imidazol-4-yl]-benzonitrile
114	(RS)-1-[5-(2-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(5-phenyl-1H-imidazol-2-ylmethyl)-piperidin-1-yl]-methanone
115	(RS)-1-[5-(3-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(5-phenyl-1H-imidazol-2-ylmethyl)-piperidin-1-yl]-methanone
116	(RS)-1-(2-Methyl-5-phenyl-thiazol-4-yl)-1-[2-(5-phenyl-1H-imidazol-2-ylmethyl)-piperidin-1-yl]-methanone
117	(RS)-1-[5-[3-(3-Dimethylamino-propoxy)-phenyl]-2-methyl-thiazol-4-yl]-1-[2-(5-phenyl-1H-imidazol-2-ylmethyl)-piperidin-1-yl]-methanone
118	(RS)-1-[5-[3-(4-Dimethylamino-butoxy)-phenyl]-2-methyl-thiazol-4-yl]-1-[2-(5-phenyl-1H-imidazol-2-ylmethyl)-piperidin-1-yl]-methanone
119	(RS)-1-[5-[3-(2-Dimethylamino-ethoxy)-phenyl]-2-methyl-thiazol-4-yl]-1-[2-(5-phenyl-1H-imidazol-2-ylmethyl)-piperidin-1-yl]-methanone
120	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-[5-(4-fluoro-phenyl)-tetrazol-2-ylmethyl]-piperidin-1-yl]-methanone
121	(RS)-1-[2-[5-(4-Fluoro-phenyl)-tetrazol-2-ylmethyl]-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone
122	(RS)-1-[4-(4-Fluoro-phenyl)-1H-pyrazol-3-yl]-1-[2-[5-(4-fluoro-phenyl)-tetrazol-2-

	ylmethyl]-piperidin-1-yl}-methanone
123	(RS)-1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-{2-[5-(4-fluoro-phenyl)-tetrazol-2-ylmethyl]-piperidin-1-yl}-methanone
124	(RS)-1-[4-(4-Fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-1-{2-[5-(4-fluoro-phenyl)-tetrazol-2-ylmethyl]-piperidin-1-yl}-methanone
144	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(4-phenyl-imidazol-1-ylmethyl)-piperidin-1-yl]-methanone
145	(RS)-1-[5-(4-Fluoro-phenyl)-thiazol-4-yl]-1-[2-(4-phenyl-imidazol-1-ylmethyl)-piperidin-1-yl]-methanone
146	(RS)-1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-[2-(4-phenyl-imidazol-1-ylmethyl)-piperidin-1-yl]-methanone
147	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[3-(4-fluoro-phenyl)-pyrazol-1-ylmethyl]-piperidin-1-yl}-methanone
148	(RS)-1-[5-Bromo-2-methoxy-phenyl]-1-{2-[3-(4-fluoro-phenyl)-pyrazol-1-ylmethyl]-piperidin-1-yl}-methanone
149	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-2H-[1,2,3]triazol-4-yl]-1-{2-[3-(4-fluoro-phenyl)-pyrazol-1-ylmethyl]-piperidin-1-yl}-methanone
150	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-oxazol-4-yl]-1-{2-[3-(4-fluoro-phenyl)-pyrazol-1-ylmethyl]-piperidin-1-yl}-methanone
151	(RS)-1-{2-[3-(4-Fluoro-phenyl)-pyrazol-1-ylmethyl]-piperidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
152	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(4-phenyl-thiazol-2-ylmethyl)-piperidin-1-yl]-methanone
153	(R)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[3-(4-phenyl-oxazol-2-ylmethyl)-morpholin-4-yl]-methanone and (S)-(R)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[3-(4-phenyl-oxazol-2-ylmethyl)-morpholin-4-yl]-methanone
154	(RS)-1-{2-[5-(2,5-Dimethyl-2H-pyrazol-3-yl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
155	(RS)-1-[2-(4,5-Diphenyl-1H-imidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
156	(RS)-1-{2-[4-(4-Fluoro-phenyl)-1-methyl-1H-imidazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
157	(RS)-1-[2-(5-Benzofuran-2-yl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(3-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
158	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(4-pyridin-2-yl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone
159	(RS)-1-{2-[5-(3,4-Difluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
160	(RS)-1-{2-[5-(3-Fluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
161	(RS)-1-[5-(4-Fluorophenyl)-2-methylthiazol-4-yl]-1-{2-[5-(4-fluorophenyl)-1H-pyrazol-3-ylmethyl]-piperidin-1-yl}-methanone
162	(RS)-1-{2-[4-(4-Fluorophenyl)-1H-imidazol-2-ylmethyl]-piperazin-1-yl}-1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]-methanone
163	1-[5-(4-Fluorophenyl)-2-methyl-thiazol-4-yl]-1-{2-[4-(4-fluorophenyl)-oxazol-2-ylmethyl]-piperazin-1-yl}-methanone

and pharmaceutically acceptable salts thereof.

Further compounds of formula (I) can be selected from:

99	(RS)-1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-{2-[4-(4-fluoro-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl}-methanone
100	(RS)-1-{2-[4-(4-Fluoro-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl}-1-[4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-methanone
101	(RS)-1-{2-[4-(4-Fluoro-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl}-1-quinolin-2-yl-

	methanone
125	(RS)-1-{2-[5-(3-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-(3-thiophen-2-yl-phenyl)-methanone
126	(RS)-1-{2-[5-(3-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-(3-thiophen-3-yl-phenyl)-methanone
127	(RS)-1-{2-[5-(3-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-(2-pyrazol-1-yl-phenyl)-methanone
128	(RS)-2'-(1-{2-[5-(3-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanoyl)-biphenyl-4-carbonitrile
129	(RS)-1-{2-[5-(3-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-(4-methoxy-biphenyl-3-yl)-methanone
130	(RS)-1-{2-[5-(3-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-(2-pyrrol-1-yl-phenyl)-methanone
131	(RS)-1-Dibenzofuran-4-yl-1-{2-[5-(3-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanone
132	(RS)-1-{2-[5-(3-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-(2-methoxy-4-methyl-phenyl)-methanone
133	(RS)-1-(2-Ethoxy-4-methyl-phenyl)-1-{2-[5-(3-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanone
134	(RS)-1-(3,5-Dichloro-2-methoxy-phenyl)-1-{2-[5-(3-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanone
135	(RS)-1-{2-[5-(3-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-(1-methoxy-naphthalen-2-yl)-methanone
136	(RS)-4-Ethoxy-2-ethyl-5-(1-{2-[5-(3-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanoyl)-benzonitrile
137	(RS)-4-Ethoxy-5-(1-{2-[5-(3-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanoyl)-2-methyl-benzonitrile
138	(RS)-1-{2-[5-(3-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-(4'-methoxy-4-nitro-biphenyl-2-yl)-methanone
139	(RS)-1-{2-[5-(3-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-(2'-methyl-4-nitro-biphenyl-2-yl)-methanone
140	(RS)-1-{2-[5-(3-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-1-(4-nitro-biphenyl-2-yl)-methanone
141	(RS)-1-Benzofuran-7-yl-1-{2-[5-(3-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanone
142	(RS)-1-(5-Bromo-4-ethyl-2-methoxy-phenyl)-1-{2-[5-(3-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl}-methanone
143	(RS)-1-[1-Ethyl-4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-1-[2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-methanone
164	(RS)-1-[3-(5-Bromo-4-phenyl-oxazol-2-ylmethyl)-morpholin-4-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
165	(RS)-1-[2-(5-Chloro-4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
166	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-(5-phenyl-4H-[1,2,4]triazol-3-ylmethyl)-pyrrolidin-1-yl]-methanone
167	(RS)-1-[2-(5-Bromo-4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
168	(RS)-1-(2-Methyl-5-phenyl-thiazol-4-yl)-1-[2-(4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone
169	(RS)-1-[1-(2-Dimethylamino-ethyl)-4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-1-[2-(4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone
170	(RS)-2-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-4-phenyl-oxazole-5-carbonitrile
171	(RS)-1-[2-(5-Bromo-4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-1-(2-methyl-5-

	phenyl-thiazol-4-yl)-methanone
172	1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-(4-phenyl-oxazol-2-ylmethyl)-pyrrolidin-1-yl]-methanone
173	1-[(S)-2-(5-Bromo-4-phenyl-oxazol-2-ylmethyl)-pyrrolidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
174	(RS)-1-[5-(4-Chloro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone
175	(RS)-1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-[2-(4-phenyl-thiazol-2-ylmethyl)-piperidin-1-yl]-methanone
176	(RS)-1-{2-[4-(2-Bromo-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone
177	(RS)-2-[2-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-oxazol-4-yl]-benzonitrile
178	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[4-(2-fluoro-phenyl)-thiazol-2-ylmethyl]-piperidin-1-yl}-methanone
179	(RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[4-(3-fluoro-phenyl)-thiazol-2-ylmethyl]-piperidin-1-yl}-methanone
180	(RS)-1-{2-[4-(3-Fluoro-phenyl)-thiazol-2-ylmethyl]-piperidin-1-yl}-1-(2-methyl-5-phenyl-thiazol-4-yl)-methanone

and pharmaceutically acceptable salts thereof.

When a halogen atom is present in the compound of formula (I) it may be fluorine, chlorine, bromine or iodine, preferably fluorine.

5 When the compound of formula (I) contains an alkyl group, whether alone or forming part of a larger group, e.g. alkoxy or alkylthio, the alkyl group may be straight chain, branched or cyclic, or combinations thereof, it is preferably methyl or ethyl.

When used herein the term aryl means a 5- to 6- membered aromatic ring, for example phenyl, or a 7 to 12 membered bicyclic ring system where at least one of the rings is aromatic, for 10 example naphthyl.

It will be appreciated that compounds of formula (I) may exist as *R* or *S* enantiomers. The present invention includes within its scope all such isomers, including mixtures. Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric 15 forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

It will be understood that the invention includes pharmaceutically acceptable derivatives of compounds of formula (I) and that these are included within the scope of the invention.

20 Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable derivatives.

As used herein "pharmaceutically acceptable derivative" includes any pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula (I) which, upon administration to the recipient is capable of providing (directly or indirectly) a compound of 25 formula (I) or an active metabolite or residue thereof.

It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be

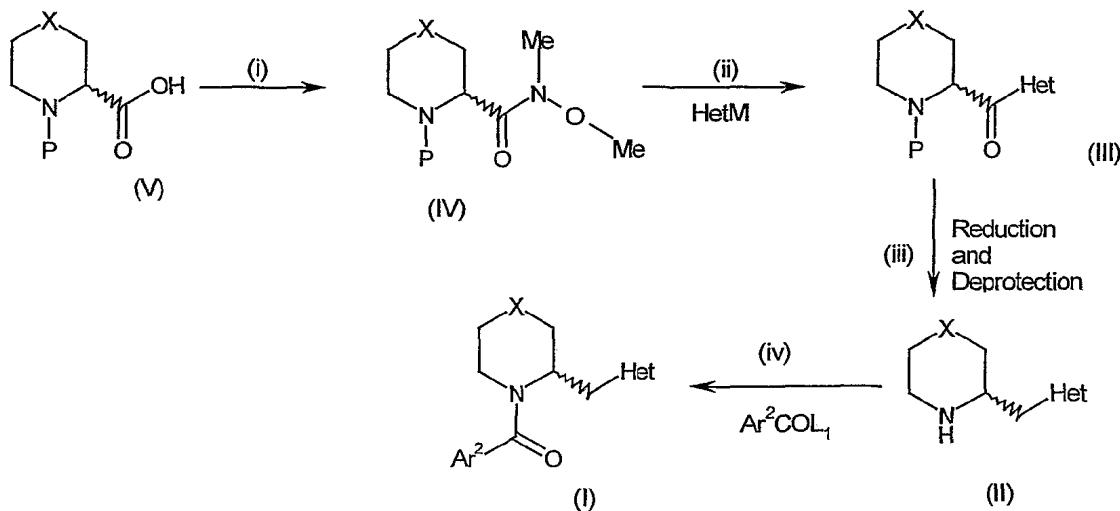
apparent to those skilled in the art and include acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other salts e.g. oxalates, may be used, for example in the isolation of 5 compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

10 Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the 15 compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

According to a further feature of the invention there is provided a process for the preparation of compounds of formula (I) and salts thereof. The following schemes detail some synthetic routes to compounds of the invention

20 **Scheme 1**



wherein X, Het and Ar² are as defined for compounds of formula (I), P is a protecting group and M is a metal, for example, lithium.

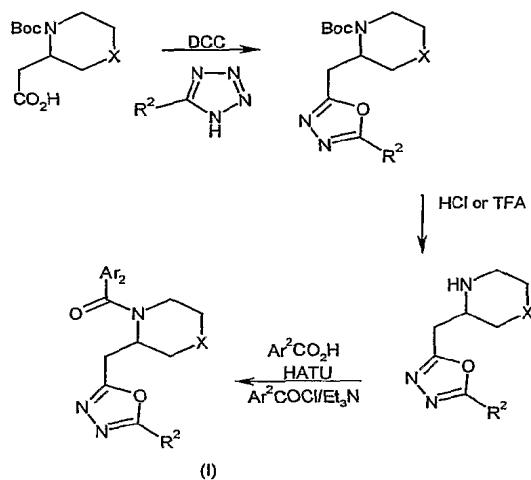
25 Examples of suitable leaving groups L¹ include halogen, OC(=O)alkyl and OC(=O)O-alkyl. The transformation (II) to (I) may be carried out in an inert solvent such as dichloromethane, in the presence of a base such as triethylamine. Alternatively this step may be carried out when L¹ represents hydroxy, in which case reaction with (II) takes place in an inert solvent such as dichloromethane in the presence of a diimide coupling reagent such as 1-ethyl-3-30 (3-dimethylaminopropyl)carbodiimide hydrochloride, and an activator such as 1-hydroxybenzotriazole.

Examples of protecting groups P include *t*-butyloxycarbonyl, trifluoroacetyl and benzoyloxycarbonyl. Deprotection conditions are respectively, acid (e.g. trifluoroacetic acid in dichloromethane), base (e.g. sodium hydroxide in a solvent such as aqueous methanol) and catalytic hydrogenolysis in an inert solvent (e.g using palladium on charcoal in a lower alcohol or ethyl acetate).

Compounds of formula (V) are known in the literature or can be prepared by known methods.

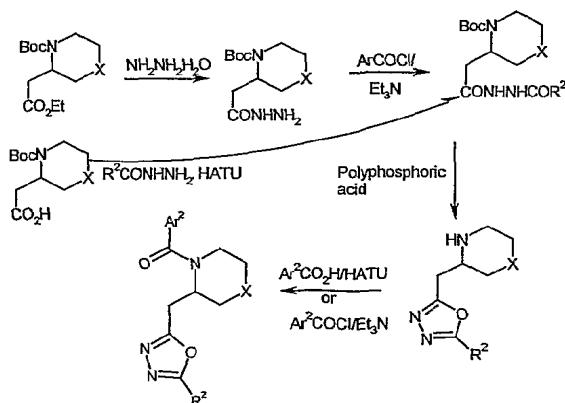
Compounds of formula (I) when Het is a 5-aryl-1,3,4-oxadiazole can be prepared by the process described in scheme 2a, or 2b, where X, Ar² and R² are as defined for compounds of formula (I).

Scheme 2a



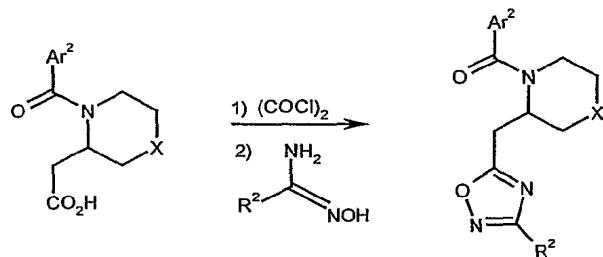
15

Scheme 2b

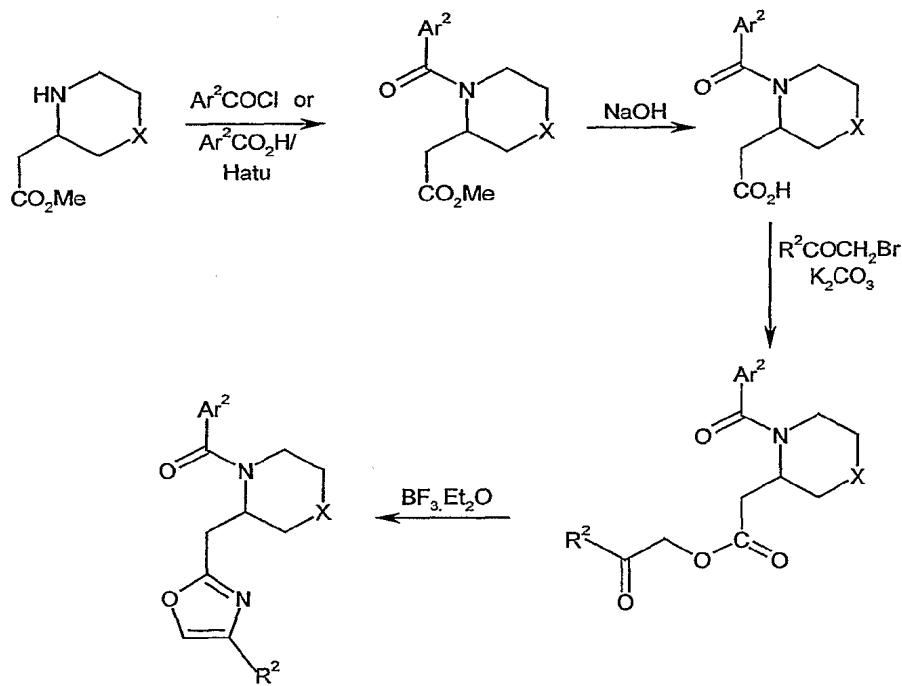


20

Compounds of formula (I) when Het is substituted 3-(1,2,4-oxadiazole) can be prepared by the process described in scheme 3 where X, Ar² and R² are as defined for compounds of formula (I).

Scheme 3

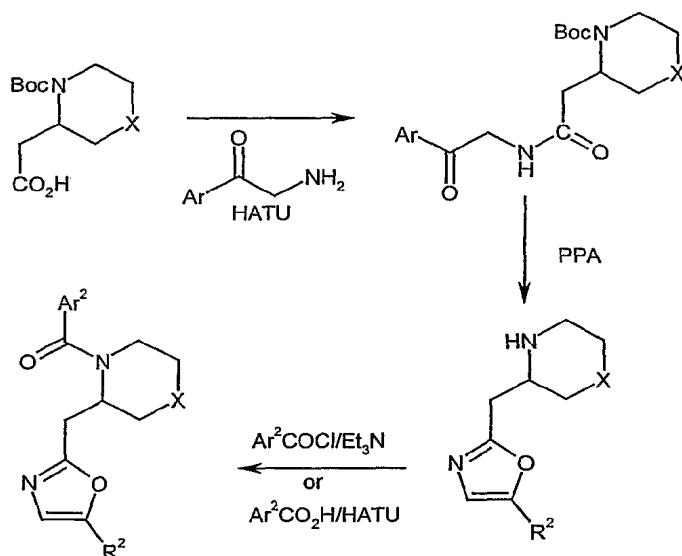
5 Compounds of formula (I) when Het is a 2-(4-aryloxazole) can be prepared by the process described in Scheme 4 where X, Ar² and R² are as defined for compounds of formula (I).

Scheme 4

10

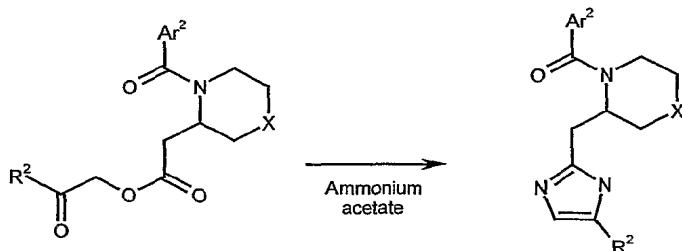
Compounds of formula (I) when Het is a 2-(5-aryloxazole) can be prepared by the process described in Scheme 5 where X, Ar² and R² are as defined for compounds of formula (I).

Scheme 5



Compounds of formula (I) where Het is a 2-(4-substituted imidazole) can be prepared by the process described in scheme 6 where X, Ar² and R² are as defined for compounds of formula (I).

5 **Scheme 6**



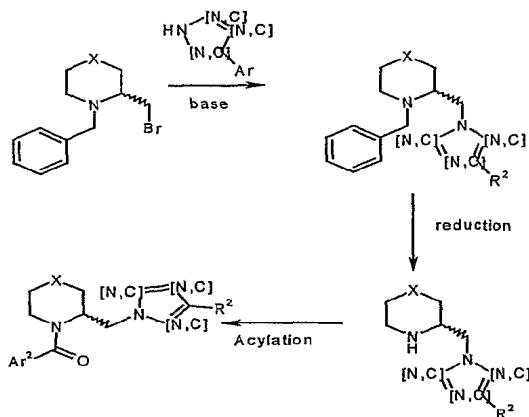
wherein Ar² X, R² are as defined for compounds of formula (I).

10

Scheme 7

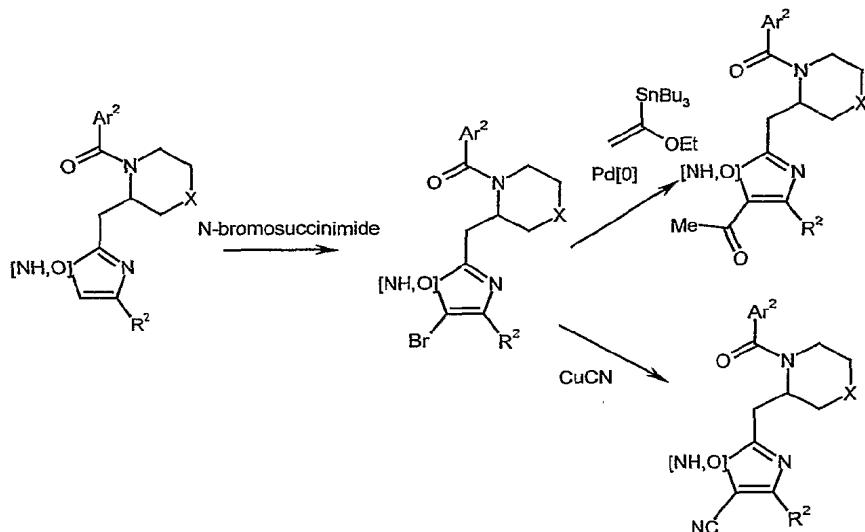
Compounds of formula (I) wherein the Het group is linked to the cyclic ring through a nitrogen in the Het group, can be prepared by the process defined in scheme 7 wherein X, Ar² and R² are as defined for compounds of formula (I).

15



Compounds wherein the Het group is substituted can be prepared by the process defined in scheme 8 wherein Ar^2 , X and R^2 are as defined for compounds of formula (I).

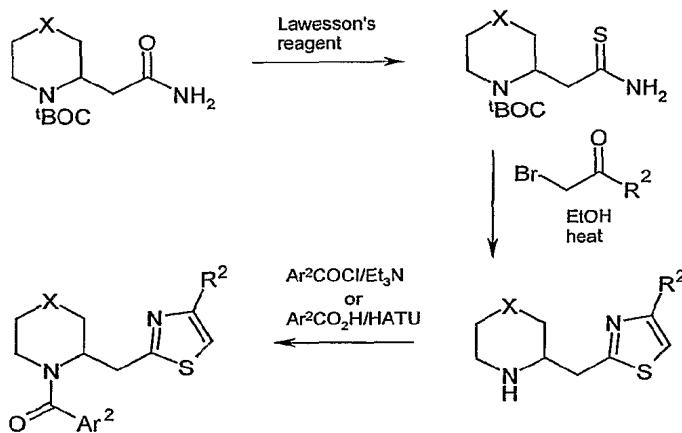
Scheme 8



5

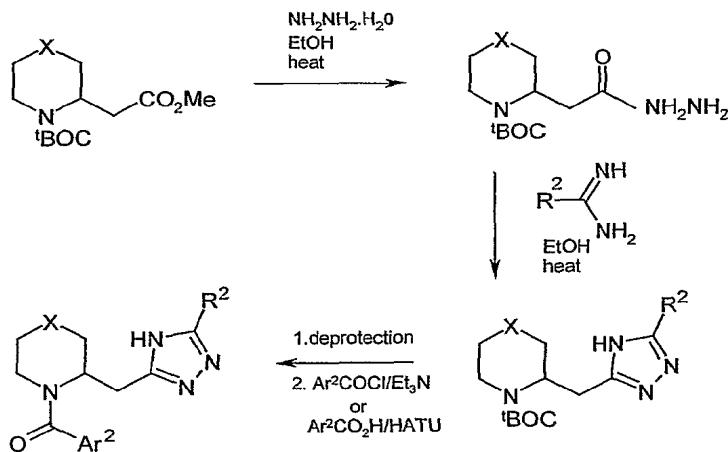
Compounds of formula (I) where Het is a 2-(4-aryltiazole) can be prepared by the process described in Scheme 9 where X, Ar^2 and R^2 are as defined for compounds of formula (I).

10 **Scheme 9**



Compounds of formula (I) where Het is a 3-(5-aryltriazole) can be prepared by the process described in Scheme 10 where X, Ar² and R² are as defined for compounds of formula (I).

5 **Scheme 10**



10 All starting materials used in the above schemes are commercially available or prepared by known literature methods.

15 The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, e.g. 5 to 1000, preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I), or pharmaceutically acceptable derivatives thereof.

20 Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are useful for the treatment of diseases or disorders where an antagonist of a human orexin receptor is

required such as obesity and diabetes; prolactinoma; hypoprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; Cushings syndrome/disease; hypothalamic-adrenal dysfunction; dwarfism; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; sleep disturbances associated with diseases 5 such as neurological disorders, neuropathic pain and restless leg syndrome; heart and lung diseases; depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delerium; dementia; bulimia and hypopituitarism. The 10 compounds of formula (I) or pharmaceutically acceptable derivatives thereof are also useful in the treatment of stroke, particularly ischemic and haemorrhagic. Furthermore the compounds of formula (I) or pharmaceutically acceptable derivatives thereof are useful in blocking the emetic response i.e. nausea and vomiting.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are 15 particularly useful for the treatment of obesity, including obesity associated with Type 2 diabetes, and sleep disorders. Additionally the compounds are useful in the the treatment of stroke and blocking the emetic response, i.e. nausea and vomiting.

Other diseases or disorders which may be treated in accordance with the invention 20 include disturbed biological and circadian rhythms; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; adrenohypophysis hypofunction; functional or psychogenic amenorrhea; adrenohypophysis hyperfunction; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; 25 arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-polio syndrome and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; and tolerance to narcotics or withdrawal from narcotics.

The invention also provides a method of treating or preventing diseases or disorders 30 where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable derivative thereof.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for use in the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

For use in therapy the compounds of the invention are usually administered as a 40 pharmaceutical composition. The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be administered by any convenient method, e.g. by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration, and the pharmaceutical compositions adapted accordingly.

5 The compounds of formula (I) and their pharmaceutically acceptable derivatives which are active when given orally can be formulated as liquids or solids, e.g. as syrups, suspensions, emulsions, tablets, capsules or lozenges.

10 A liquid formulation will generally consist of a suspension or solution of the active ingredient in a suitable liquid carrier(s) e.g. an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations, such as magnesium stearate, starch, lactose, sucrose and cellulose.

15 A composition in the form of a capsule can be prepared using routine encapsulation procedures, e.g. pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), e.g. aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

20 Typical parenteral compositions consist of a solution or suspension of the active ingredient in a sterile aqueous carrier or parenterally acceptable oil, e.g. polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

25 Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active ingredient in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a disposable dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas e.g. air, or an organic propellant such as a fluorochlorohydrocarbon or hydrofluorocarbon. Aerosol dosage forms can also take the form of pump-atomisers.

30 Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles where the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

35 Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

40 Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

The dose of the compound of formula (I), or a pharmaceutically acceptable derivative thereof, used in the treatment or prophylaxis of the abovementioned disorders or diseases will vary in the usual way with the particular disorder or disease being treated, the weight of the subject and other similar factors. However, as a general rule, suitable unit doses may be 0.05 to

1000 mg, more suitably 0.05 to 500 mg. Unit doses may be administered more than once a day for example two or three times a day, so that the total daily dosage is in the range of about 0.01 to 100 mg/kg; and such therapy may extend for a number of weeks or months. In the case of pharmaceutically acceptable derivatives the above figures are calculated as the parent compound 5 of formula (I).

No toxicological effects are indicated/expected when a compound of formula (I) is administered in the above mentioned dosage range.

Human orexin-A has the amino acid sequence:

pyroGlu Pro Leu Pro Asp Cys Cys Arg Gln Lys Thr Cys Ser Cys Arg Leu
10 1 5 10 15
Tyr Glu Leu Leu His Gly Ala Gly Asn His Ala Ala Gly Ile Leu Thr
20 25 30
Leu-NH₂

Orexin-A can be employed in screening procedures for compounds which inhibit the 15 ligand's activation of the orexin-1 receptor.

In general, such screening procedures involve providing appropriate cells which express the orexin-1 receptor on their surface. Such cells include cells from mammals, yeast, *Drosophila* or *E. coli*. In particular, a polynucleotide encoding the orexin-1 receptor is used to transfect cells 20 to express the receptor. The expressed receptor is then contacted with a test compound and an orexin-1 receptor ligand to observe inhibition of a functional response. One such screening procedure involves the use of melanophores which are transfected to express the orexin-1 receptor, as described in WO 92/01810.

Another screening procedure involves introducing RNA encoding the orexin-1 receptor 25 into *Xenopus* oocytes to transiently express the receptor. The receptor oocytes are then contacted with a receptor ligand and a test compound, followed by detection of inhibition of a signal in the case of screening for compounds which are thought to inhibit activation of the receptor by the ligand.

Another method involves screening for compounds which inhibit activation of the 30 receptor by determining inhibition of binding of a labelled orexin-1 receptor ligand to cells which have the receptor on their surface. This method involves transfecting a eukaryotic cell with DNA encoding the orexin-1 receptor such that the cell expresses the receptor on its surface and contacting the cell or cell membrane preparation with a compound in the presence of a labelled form of an orexin-1 receptor ligand. The ligand may contain a radioactive label. The amount of labelled ligand bound to the receptors is measured, e.g. by measuring radioactivity.

35 Yet another screening technique involves the use of FLIPR equipment for high throughput screening of test compounds that inhibit mobilisation of intracellular calcium ions, or other ions, by affecting the interaction of an orexin-1 receptor ligand with the orexin-1 receptor.

All publications, including but not limited to patents and patent applications, cited in this 40 specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Examples illustrate the preparation of pharmacologically active compounds of the invention. The Descriptions D1-D57 illustrate the preparation of intermediates to compounds of the invention.

In the Examples ^1H NMR's were measured at 250MHz in CDCl_3 unless otherwise stated.

5 The following abbreviations are used herein;

PyBop means benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate

THF means tetrahydrafuran

EDC.HCL means 1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride.

DMF means N,N-dimethylformamide

10 HATU means O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

The following Examples illustrate the preparation of pharmacologically active compounds of the invention. The Descriptions D1-D123 illustrate the preparation of intermediates to compounds of the invention.

15

**Description 1 (RS)-2-(5-Phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidine-1-carboxylic acid
tert butyl ester**

A mixture of 2-carboxymethyl-piperidine-1-carboxylic acid *tert* butyl ester (1.22g), (Peschke, Bernd; Ankersen, Michael; Hansen, Birgit Sehested; Hansen, Thomas Kruse; Johansen, Nils Langeland; Lau, Jesper; Madsen, Kjeld; Petersen, Hans; Thogersen, Henning; Watson, Brett. *Eur. J. Med. Chem.* (1999), 34(5), 363-380), dicyclohexylcarbodiimide (1.05g) and 5-phenyltetrazole (0.73g) in toluene (25ml) was heated at 100°C for 3h. The reaction mixture was cooled to room temperature, diluted with diethyl ether and solvent decanted from the precipitated gum. The gum was column chromatographed (silica gel, 0 – 50% ethyl acetate in pentane eluant) to give the title compound (1.1g).

Mass Spectrum (API $^+$): Found 344 (MH $^+$). $\text{C}_{19}\text{H}_{25}\text{N}_3\text{O}_3$ requires 343.

^1H NMR δ : (CDCl_3) 1.31 (9H, s), 1.43 – 1.69 (6H, m), 2.95 (1H, t), 3.09 (1H, dd), 3.30 (1H, dd), 4.11 (1H, br. s), 4.79 (1H, br. s.), 7.51 (3H, m) and 8.05 (2H, m).

30

Description 2 (RS)-2-(5-Phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidine

A solution of (RS)-2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidine-1-carboxylic acid *tert* butyl ester (0.175g) in dichloromethane (4ml) was cooled (ice bath) and treated with trifluoroacetic acid (1ml). The mixture was stirred for 1h, added to saturated potassium carbonate and the product extracted into dichloromethane. The organic phase was dried (MgSO_4) and solvent removed at reduced pressure to give the title compound (0.115g)

Mass Spectrum (API $^+$): Found 244 (MH $^+$). $\text{C}_{14}\text{H}_{16}\text{F}_3\text{N}_3\text{O}$ requires 243.

^1H NMR δ : (CDCl_3) 1.18 – 1.85 (6H, m), 2.68 (1H, m), 2.97 (2H, m), 3.10 (2H, m), 7.55 (3H, m) and 8.05 (2H, m).

40

Description 3 (RS)-2-[5-(3-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidine-1-carboxylic acid *tert* butyl ester

The title compound ((1.28g) was prepared from 2-carboxymethyl-piperidine-1-carboxylic acid tert butyl ester (1.48g), 5-(3-fluorophenyl)tetrazole (1.0g) and dicyclohexylcarbodiimide (1.25g) according to the method of description 1.

Mass Spectrum (API⁺): Found 362 (MH⁺). C₁₉H₂₄FN₃O₃ requires 361.

5

Description 4 (RS)-2-[5-(3-Fluoro-phenyl-[1,3,4]oxadiazol-2-ylmethyl]-piperidine

The title compound (0.81g) was prepared from the compound of description 3 (1.27g) according to the method of description 2.

Mass Spectrum (API⁺): Found 262 (MH⁺). C₁₄H₁₆FN₃O₃ requires 261.

10 ¹H NMR δ: (CDCl₃) 1.38 – 1.84 (6H, m), 2.71 (1H, m), 3.02 (2H, m), 3.14(2H, m), 7.22 (1H, dd), 7.48 (1H, m), 7.73 (1H, dd) and 7.83 (1H, dd).

Description 5 (RS)-2-[5-(3-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidine-1-carboxylic acid tert butyl ester

15 The title compound (1.21g) was prepared from 2-carboxymethyl-piperidine-1-carboxylic acid tert butyl ester (1.35g), 5-(3-chlorophenyl)tetrazole (1.0g) and dicyclohexylcarbodiimide (1.15g) according to the method of description 1.

Mass Spectrum (API⁺): Found 378 (MH⁺). C₁₉H₂₄ClN₃O₃ requires 377.

20 **Description 6 (RS)-2-[5-(3-Chloro-phenyl-[1,3,4]oxadiazol-2-ylmethyl]-piperidine**

The title compound (0.89g) was prepared from the compound of description 5 (1.21g) according to the method of description 2.

Mass Spectrum (API⁺): Found 278 (MH⁺). C₁₄H₁₆ClN₃O requires 277.

25 ¹H NMR δ: (CDCl₃) 1.43 – 1.90 (6H, m), 2.79 (1H, m), 3.05 – 3.18 (2H, m), 3.27 (2H, m), 7.40 – 7.52 (2H, m), 7.91 (1H, dd) and 8.00 (1H, d).

Description 7 (RS)-2-(5-Pyridin-2-yl-[1,3,4]oxadiazol-2-ylmethyl)-piperidine-1-carboxylic acid tert butyl ester

30 The title compound (1.39g) was prepared from 2-carboxymethyl-piperidine-1-carboxylic acid tert butyl ester (1.65g), 5-(pyridin-2-yl)tetrazole (1.0g) and dicyclohexylcarbodiimide (1.43g) according to the method of description 1.

Mass Spectrum (API⁺): Found 345 (MH⁺). C₁₈H₂₄N₄O₃ requires 344.

Description 8 (RS)-2-(5-Piperidin-2-ylmethyl-[1,3,4]oxadiazol-2-yl)-pyridine

35 The title compound (0.89g) was prepared from the compound of description 7 (1.39g) according to the method of description 2.

Mass Spectrum (API⁺): Found 245 (MH⁺). C₁₃H₁₆N₄O requires 244.

¹H NMR δ: (CDCl₃) 1.49 – 1.90 (6H, m), 2.72 – 2.82 (2H, m), 3.07 – 3.29 (4H, m), 7.44 – 7.49 (1H, m), 7.85 – 7.92 (1H, m), 8.22 (1H, dd) and 8.76 (1H, dd).

40

Description 9 (RS)-2-[5-(4-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidine-1-carboxylic acid tert butyl ester

The title compound (1.34g) was prepared from 2-carboxymethyl-piperidine-1-carboxylic acid tert butyl ester (1.22g), 5-(4-fluorophenyl)tetrazole (0.82g) and dicyclohexylcarbodiimide (1.05g) according to the method of description 1.

Mass Spectrum (API⁺): Found 362 (MH⁺). C₁₉H₂₄FN₃O₃ requires 361.

5

Description 10 (RS)-2-[5-(4-Fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidine

The title compound (0.73g) was prepared from the compound of description 9 (1.2g) according to the method of description 2.

Mass Spectrum (API⁺): Found 262 (MH⁺). C₁₄H₁₆FN₃O₃ requires 261.

10

¹H NMR δ: (CDCl₃) 1.25 – 1.84 (6H, m), 2.68 (1H, m), 2.96 (2H, m), 3.07 (2H, m), 7.12 – 7.27 (3H, m) and 8.04 (2H, m).

Description 11 (RS)-2-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidine-1-carboxylic acid tert butyl ester

15

The title compound (1.65g) was prepared from 2-carboxymethyl-piperidine-1-carboxylic acid tert butyl ester (1.26g), 5-(4-chlorophenyl)tetrazole (1.08g) and dicyclohexylcarbodiimide (1.15g) according to the method of description 1.

Mass Spectrum (API⁺): Found 378, 380 (MH⁺). C₁₉H₂₄ClN₃O₃ requires 377, 379.

20

Description 12 (RS)-2-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidine

The title compound (0.89g) was prepared from the compound of description 11 (1.21g) according to the method of description 2.

Mass Spectrum (API⁺): Found 278, 280 (MH⁺). C₁₄H₁₆ClN₃O requires 277, 279.

25

¹H NMR δ: (CDCl₃) 1.43 – 1.90 (6H, m), 2.79 (1H, m), 3.05 – 3.18 (2H, m), 3.27 (2H, m), 7.40 – 7.52 (2H, m), 7.91 (1H, dd) and 8.00 (1H, d).

Description 13 (RS)-2-[5-(2-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidine-1-carboxylic acid tert butyl ester

30

The title compound (1.65g) was prepared from 2-carboxymethyl-piperidine-1-carboxylic acid tert butyl ester (1.35g), 5-(2-chlorophenyl)tetrazole (1.0g) and dicyclohexylcarbodiimide (1.16g) according to the method of description 1.

Mass Spectrum (API⁺): Found 378, 380 (MH⁺). C₁₉H₂₄ClN₃O₃ requires 377, 379.

Description 14 (RS)-2-[5-(2-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidine

35

The title compound (1.10g) was prepared from the compound of description 13 (1.48g) according to the method of description 2.

Mass Spectrum (API⁺): Found 278, 280 (MH⁺). C₁₄H₁₆ClN₃O requires 277, 279.

¹H NMR δ: (CDCl₃) 1.11 – 1.85 (6H, m), 2.69 (1H, m), 3.00 (2H, m), 3.10 (2H, m), 7.38 (1H, t), 7.46 (1H, t), 7.54 (1H, dd) and 7.97 (1H, dd).

40

Description 15 (RS)-2-[5-(2, 3-Dichloro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidine-1-carboxylic acid tert butyl ester

The title compound (0.70g) was prepared from 2-carboxymethyl-piperidine-1-carboxylic acid tert butyl ester (1.13g), 5-(2, 3-dichlorophenyl)tetrazole (1.0g) and dicyclohexylcarbodiimide (0.98g) according to the method of description 1.

Mass Spectrum (API⁺): Found 412, 414 (MH⁺). C₁₉H₂₃Cl₂N₃O₃ requires 411, 413.

5

Description 16 (RS)-2-[5-(2, 3-Dichlorophenyl-[1,3,4]oxadiazol-2-ylmethyl]-piperidine

The title compound (0.47g) was prepared from the compound of description 15 (0.62g) according to the method of description 2.

Mass Spectrum (API⁺): Found 312, 314 (MH⁺). C₁₄H₁₅Cl₂N₃O requires 311, 313.

10 ¹H NMR δ: (CDCl₃) 1.26 – 1.82 (6H, m), 2.69 (1H, m), 3.01 (2H, m), 3.10 (2H, m), 7.33 (1H, t), 7.66 (1H, dd) and 7.86 (1H, dd).

Description 17 (RS)-2-Hydrazinocarbonylmethyl-piperidine-1-carboxylic acid tert butyl ester.

2-Methoxycarbonylmethyl-piperidine-1-carboxylic acid tert butyl ester (8.14g) in ethanol (150ml) was treated with hydrazine hydrate (19ml) and the mixture boiled for 16h. Solvent was removed at reduced pressure and the residue azeotroped with toluene to give the title compound (8.34g)
¹H NMR δ: (CDCl₃) 1.47 (9H, s), 1.62 (6H, m), 2.34 – 2.42 (2H, m), 2.59 – 2.85 (3H, m), 3.85 (1H, br. s.), 3.97 (1H, br. s.) and 4.62 (1H, br. s.).

20 **Description 18 (RS)-2-(2-{N'-(1-(2-Fluoro-phenyl)-methanoyl]-hydrazino}-2-oxo-ethyl)-piperidine-1-carboxylic acid tert butyl ester**

To a solution of the compound of description 17 (1.0g) in pyridine (10ml), 2-fluorobenzoyl chloride (0.62g) was added. The mixture was stirred for 2h, diluted with water and the milky solution extracted with ethyl acetate (x 2). The combined organic phase was washed with brine, dried (MgSO₄) and solvent removed at reduced pressure. The residue was triturated with pentane to give after drying under reduced pressure at 35°C, the title compound (1.4g).

Mass Spectrum (API⁺): Found 380 (MH⁺). C₁₉H₂₆FN₃O₄ requires 379.

Description 19 (RS)-2-[5-(2-Fluoro-phenyl-[1,3,4]oxadiazol-2-ylmethyl]-piperidine

30 The benzoyl hydrazide of description 18 (0.2g) was added to polyphosphoric acid (2g) at 45°C, the reaction temperature was increased to 150°C and heating continued for 2h. The reaction mixture was poured onto potassium carbonate in crushed iced and the mixture extracted with dichloromethane (x 3). The combined organic extracts were washed with brine, dried (MgSO₄) and solvent removed at reduced pressure to give the title compound (0.08g) as a yellow oil.

35 Mass Spectrum (API⁺): Found 262 (MH⁺). C₁₄H₁₆FN₃O₃ requires 261.

Description 20 (RS)-(2-{N'-(1-Benzofuran-4-yl-methanoyl)-hydrazino}-2-oxo-ethyl)-piperidine-1-carboxylic acid tert butyl ester

A mixture of benzofuran-4-carboxylic acid (0.90g), diisopropylethylamine (3.2ml) and [O-(7-40 azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (2.09g) in dimethylformamide (20ml) was stirred for 15 min and then treated with the benzoyl hydrazide of description 17 (1.43g). The mixture was stirred for 16h, diluted with water and extracted with diethyl ether. The ether extract was washed with water (x 3), dried (MgSO₄) and solvent removed

at reduced pressure. The residue was suspended in a mixture of diethyl ether/dichloromethane (30ml, 2:1) to give the title compound (1.29g) as a colourless solid.

Mass Spectrum (API⁺): Found 402 (MH⁺). C₂₁H₂₇N₃O₅ requires 401

5 **Description 21 (RS)-2-(5-Benzofuran-4-yl-[1,3,4]oxadiazol-2-ylmethyl)-piperidine**

The title compound (0.1g) was prepared from the compound of description 20 (0.2g) according to the method of description 19. The obtained compound was used without further purification.

Mass Spectrum (API⁺): Found 284 (MH⁺). C₁₆H₁₇N₃O₂ requires 283

10 **Description 22 (RS)-2-(2-{N'-[1-(2, 3-Difluoro-phenyl)-methanoyl]-hydrazino}-2-oxo-ethyl)-piperidine-1-carboxylic acid tert butyl ester**

The title compound (1.15g) was prepared from the compound of description 17 (1.0g) and 2,3-difluorobenzoyl chloride (0.49ml) according to the method of description 18.

Mass Spectrum (API⁺): Found 398 (MH⁺). C₁₉H₂₅F₂N₃O₄ requires 397

15

Description 23 (RS)-2-[5-(2,3-Difluoro-phenyl-[1,3,4]oxadiazol-2-ylmethyl]-piperidine

The title compound (0.70g) was prepared from the compound of description 22 (1.1g) according to the method of description 19. The compound was used without further purification.

Mass Spectrum (API⁺): Found 280 (MH⁺). C₁₄H₁₅F₂N₃O requires 279.

20

Description 24 (RS)-2-(2-{N'-[1-(2, 5-Difluoro-phenyl)-methanoyl]-hydrazino}-2-oxo-ethyl)-piperidine-1-carboxylic acid tert butyl ester

The title compound (1.50g) was prepared from the compound of description 17 (1.0g) and 2,5-difluorobenzoyl chloride (0.49ml) according to the method of description 18.

25

Mass Spectrum (API⁺): Found 398 (MH⁺). C₁₉H₂₅F₂N₃O₄ requires 397

Description 25 (RS)-2-[5-(2,5-Difluoro-phenyl-[1,3,4]oxadiazol-2-ylmethyl]-piperidine

The title compound (0.83g) was prepared from the compound of description 24 (1.5g) according to the method of description 19.

30

Mass Spectrum (API⁺): Found 280 (MH⁺). C₁₄H₁₅F₂N₃O requires 279.

¹H NMR δ: (CDCl₃) 1.28 – 1.82 (6H, m), 2.63 – 2.74 (1H, m), 2.97 – 3.11 (4H, m), 7.20 – 7.31 (3H, m).

35

Description 26 (RS)-2-(2-{N'-[1-(3, 5-Difluoro-phenyl)-methanoyl]-hydrazino}-2-oxo-ethyl)-piperidine-1-carboxylic acid tert butyl ester

The title compound (0.79g) was prepared from the compound of description 17 (1.0g) and 3,5-difluorobenzoic acid (0.62) according to the method of description 20.

Mass Spectrum (API⁺): Found 398 (MH⁺). C₁₉H₂₅F₂N₃O₄ requires 397

40

¹H NMR δ: (CDCl₃) 1.45 (9H, s), 1.66 (6H, s), 2.52 – 2.87 (3H, m), 3.98 (1H, d), 4.72 (1H, m), 6.96 (1H, m) and 7.34 (2H, m).

Description 27 (RS)-2-[5-(3,5-Difluoro-phenyl-[1,3,4]oxadiazol-2-ylmethyl]-piperidine

The title compound (0.44g) was prepared from the compound of description 26 (0.79g) according to the method of description 19. The compound was used without further purification.

Mass Spectrum (API⁺): Found 280 (MH⁺). C₁₄H₁₅F₂N₃O requires 279.

5 **Description 28 (RS)-2-(2-{N'-[1-(6-Methyl-pyridin-2-yl)-methanoyl]-hydrazino}-2-oxo-ethyl)-piperidine-1-carboxylic acid tert butyl ester**

The title compound (1.18g) was prepared from the compound of description 17 (1.50g) and 6-methylpicolinic acid (0.79g) according to the method of description 20.

Mass Spectrum (API⁺): Found 377 (MH⁺). C₁₉H₂₈N₄O₄ requires 376

10

Description 29 (RS)-2-Methyl-6-(5-piperidin-2-ylmethyl-[1,3,4]oxadiazol-2-yl)-pyridine

The title compound (0.60g) was prepared from the compound of description 28 (1.17g) according to the method of description 19. The compound was used without further purification.

Mass Spectrum (API⁺): Found 259 (MH⁺). C₁₄H₁₈N₄O requires 258.

15

Description 30 (RS)-2-{2-[N'-(1-Furan-2-yl-methanoyl)-hydrazino]-2-oxo-ethyl}-piperidine-1-carboxylic acid tert butyl ester.

2-Carboxymethyl-piperidine-1-carboxylic acid tert butyl ester (2.0g) was added to [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (3.13g) in 20 dimethylformamide (10ml) containing diisopropylethylamine (3.2g) and the mixture stirred for 15min. 2-Furoic acid hydrazide (1.04g) was then added and stirring continued for 16h. The reaction mixture was diluted with water and extracted with diethyl ether. The combined ether extracts were washed with water, dried and solvent removed at reduced pressure. the residue was column chromatographed (silica gel, 20 – 50% ethyl acetate/hexane) to give the title compound (2.05g).

Mass Spectrum (API⁺): Found 352 (MH⁺). C₁₇H₂₅N₃O₅ requires 351.

Description 31 (RS)-2-(5-Furan-2-yl-[1,3,4]oxadiazol-2-ylmethyl)-piperidine

The title compound (0.40g) was prepared from the compound of description 30 (1.0g) according to the method of description 19. The compound was used without further purification.

Mass Spectrum (API⁺): Found 234 (MH⁺). C₁₂H₁₅N₃O₂ requires 233.

¹H NMR δ: (CDCl₃) 1.09 – 1.71 (6H, m), 2.42– 2.56 (3H, m), 2.89 (2H, m), 6.79 (1H, m), 7.30 (1H, m) and 8.03 (1H, m)

35 **Description 32 (S)-2-(5-Phenyl-[1,3,4]oxadiazol-2-ylmethyl)-pyrrolidine-1-carboxylic acid tert butyl ester**

The title compound was prepared from (S)-2-carboxymethyl-pyrrolidine-1-carboxylic acid tert butyl ester (2.50) and 5-phenyltetrazole (1.59g) according to the method of description 1.

Mass Spectrum (API⁺): Found 330 (MH⁺). C₁₈H₂₃N₃O₃ requires 329.

40 ¹H NMR δ: (CDCl₃) 1.49 (9H, s), 1.81-1.88 (2H, m), 2.17 – 2.25 (2H, m), 2.40 and 3.09 (1H, m), 3.35 – 3.73 (3H, m), 4.28, 5.12 (1H, m), 7.50 (3H, m) and 8.03 (2H, m).

Description 33 2-Phenyl-5-(S)-1-pyrrolidin-2-ylmethyl-[1,3,4]oxadiazole

The title compound (1.85g) was prepared from the compound of description 32 (2.45g) according to the method of description 2.

Mass Spectrum (API⁺): Found 230 (MH⁺). C₁₃H₁₅N₃O requires 229.

5 ¹H NMR δ: (CDCl₃) 1.58–1.69 (2H, m), 1.76 – 1.97 (2H, m), 2.04 – 2.36 (1H, m), 2.99 – 3.23 (4H, m), 3.69 – 3.80 (1H, m), 7.45 – 7.57 (3H, m) and 8.01 – 8.05 (2H, m).

Description 34 (RS)-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-acetic acid methyl ester

10 The title compound (2.1g) was prepared from piperidin-2-yl-acetic acid methyl ester (3.4g) and 2-methyl-5-(4-fluorophenyl)-thiazole-4-carboxylic acid (2.20g) according to the method of description 20.

Mass Spectrum (API⁺): Found 377 (MH⁺). C₁₉H₂₁FN₂O₃S requires 376.

15 **Description 35 (RS)-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-acetic acid**

The compound of description 34 (3.4g) in methanol (75ml) was treated with water (25ml) containing sodium hydroxide (0.74g). The mixture was stirred for 16h, solvent removed at reduced pressure, the residue dissolved in water and washed with diethyl ether. The aqueous phase was acidified with 5N hydrochloric acid and extracted with ethyl acetate. The organic phase was dried (MgSO₄) and solvent removed at reduced pressure. The residue was triturated with pentane and dried in vacuo to give the title compound (2.95g)

Mass Spectrum (API⁺): Found 363 (MH⁺). C₁₈H₁₉FN₂O₃S requires 362

25 **Description 36 (RS)-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-acetic acid 2-(4-fluoro-phenyl)-2-oxo-ethyl ester**

The acid of description 35 (0.4g) was dissolved in dimethylformamide (10ml) containing potassium carbonate (0.179g) and 2-bromo-4'-fluoroacetophenone (0.24g) and the mixture stirred for 16h. Water (20ml) was added and the mixture extracted with ethyl acetate. The organic phase was washed with water, dried (MgSO₄) and solvent removed at reduced pressure to give the title compound (0.51g).

Mass Spectrum (API⁺): Found 499 (MH⁺). C₂₆H₂₄F₂N₂O₄S requires 498

30 ¹H NMR δ: (CDCl₃) (doubling of signals due to restricted rotation) 1.41 – 1.88 (6H, m), 2.49 – 2.92, 3.37 (4H, m), 2.68, 2.69 (3H, s), 4.15, 4.67 (1H, m), 5.13 – 5.31 (2H, m), 7.05 (2H, m), 7.17 (2H, m), 7.44 – 7.54 (2H, m) and 7.88 – 7.98 (2H, m).

Description 37 (RS)-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-acetic acid 2-(2-methoxyphenyl)-2-oxo-ethyl ester

35 The title compound (0.51g) was prepared from the acid of description 35 (0.40g) and 2-bromo-4'-methoxyacetophenone (0.25g) according to the method of description 36.

Mass Spectrum (API⁺): Found 511 (MH⁺). C₂₇H₂₇FN₂O₅S requires 510.

Description 38 (RS)-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-acetic acid 2-(3-fluoro-phenyl)-2-oxo-ethyl ester

The title compound (0.32g) was prepared from the acid of description 35 (0.40g) and 2-bromo-3'-fluoroacetophenone (0.24g) according to the method of description 36.

5 Mass Spectrum (API⁺): Found 499 (MH⁺). C₂₆H₂₄F₂N₂O₄S requires 498

Description 39 (RS)-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-acetic acid 2-(2-fluoro-phenyl)-2-oxo-ethyl ester

The title compound (0.32g) was prepared from the acid of description 35 (0.40g) and 2-bromo-2'-fluoroacetophenone (0.24g) according to the method of description 36.

10 Mass Spectrum (API⁺): Found 499 (MH⁺). C₂₆H₂₄F₂N₂O₄S requires 498

Description 40 (1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-acetic acid 1-methyl-2-oxo-2-phenyl-ethyl ester

15 The title compound (0.452g) was prepared from the acid of description 35 (0.40g) and 2-bromopropiophenone (0.234g) according to the method of description 36.

Mass Spectrum (API⁺): Found 495 (MH⁺). C₂₇H₂₇FN₂O₄S requires 494

Description 41: (RS)-1-(*tert*-butyloxycarbonyl)-2-(N-methoxy-N-methylcarbamoyl)piperidine

To (RS)-1-(*tert*-butyloxycarbonyl)-2-piperidine carboxylic acid (5.32 g, 23.2 mmol) in dichloromethane (20 ml) was added sequentially N,O-dimethyl hydroxylamine hydrochloride (2.68 g, 27.5 mmol), triethylamine (12 ml, 86.0 mmol) and py-BOP (13.2 g, 25.4 mmol). The resultant mixture was stirred at ambient temperature for 6 h, then diluted with dichloromethane (350 ml) and poured into 1M HCl (50 ml).

The organic phase was separated and washed with saturated aqueous sodium hydrogen carbonate (3 x 50 ml) and brine (50 ml) and then evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 20 % ethyl acetate in hexane to give the title compound as a colourless oil (3.09 g, 49 %).

30 Mass spectrum (API⁺): 273 (MH⁺). C₁₃H₂₄N₂O₄ requires 272.

Description 42: (RS)-1-(*tert*-butyloxycarbonyl)-2-((5-(4-fluorophenyl)-furan-2-yl)carbonyl)piperidine

To a stirred solution of 2-(4-fluorophenyl)-furan (1.8 g, 11.1 mmol) in THF (100 ml) at -35 °C was added *n*-butyl lithium (2.5M in THF) (4.54 ml, 11.4 mmol) over 3 min. The resultant mixture was stirred for 10 min. at -35 °C and then (RS)-1-(*tert*-butyloxycarbonyl)-2-(N-methoxy-N-methylcarbamoyl)piperidine (3.09 g, 11.4 mmol) in THF (10 ml) was added over 1 min. The resultant solution was stirred for 15 min. at -35 °C and then poured into saturated ammonium chloride (120 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organics were washed with saturated aqueous sodium hydrogen carbonate (50 ml) and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 10 % ethyl acetate in hexane to give the title compound as a golden oil (3.59 g, 85 %).

Mass spectrum (API⁺): 374 (MH⁺). C₂₁H₂₄NO₄F requires 373.

Description 43: (RS)-2-(5-(4-Fluorophenyl)-furan-2-ylmethyl)-piperidine

To a solution of (RS)-1-(*tert*-butyloxycarbonyl)-2-((5-(4-fluorophenyl)-furan-2-

5 yl)carbonyl)piperidine (2.0 g, 5.36 mmol) in diethylene glycol (20 g), was added hydrazine hydrate (0.31 ml, 5.36 mmol) and the resultant mixture heated at 100 °C for 30 min. After cooling to room temperature, potassium hydroxide (1.0 g, 17.8 mmol) was added and the mixture heated at 200 °C for 18 h. The reaction mixture was then poured into water (100 ml) and extracted with diethyl ether (3 x 75 ml). The combined organic extracts were dried (Na₂SO₄) and

10 evaporated *in vacuo* to give the title compound as a brown oil (0.88 g, 63 %).

Mass spectrum (API⁺): 260 (MH⁺). C₁₆H₁₈FNO requires 259.

Description 44: (RS)-2-(2-Oxo-2-phenyl-ethoxycarbonylmethyl)-piperidine-1-carboxylic acid *tert* butyl ester

15 2-Carboxymethyl-piperidine-1-carboxylic acid *tert* butyl ester (2.86g) and sodium carbonate (0.62g) were dissolved in water (30ml) using gentle warming. A solution of 2-

bromoacetophenone (2.33g) in ethanol (60ml) was then added and the mixture boiled for 2h. the mixture was cooled to room temperature and stood for 16h. The mixture was again boiled for 2h. solvent removed at reduced pressure and the residue partitioned between water and ethyl acetate.

20 The organic phase was dried (MgSO₄) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 1:1 ethyl acetate:pentane) to give the title compound (3.14g).

Mass spectrum (API⁺): 362 (MH⁺). C₁₉H₂₇NO₅ requires 361.

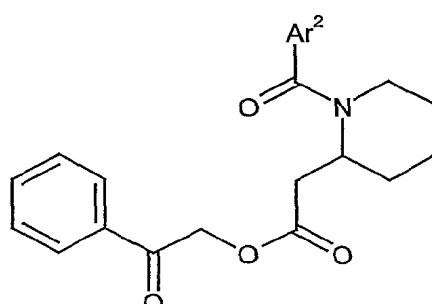
25 **Description 45 (RS)-Piperidin-2-yl-acetic acid 2-oxo-2-phenyl-ethyl ester**

The title compound (0.68g) was prepared from the compound of description 44 (0.80g) according to the method of description 2.

Mass spectrum (API⁺): 262 (MH⁺). C₁₄H₁₈NO₅ requires 261.

30 **Descriptions 46 – 49**

The compounds of descriptions 46 – 49 were prepared from the compound of description 45 (1 mole) and the corresponding carboxylic acid (1mole) according to the method of description 1.



Description	Ar ²	yield %	Mass Spectrum (Electrospray LC/MS)
46		44	Found 464 (MH ⁺). C ₂₆ H ₂₆ FN ₃ O ₄ . requires 463
47		54	Found 465 (MH ⁺). C ₂₅ H ₂₅ FN ₄ O ₄ . requires 464
48		40	Found 416 (MH ⁺). C ₂₆ H ₂₅ NO ₄ . requires 415
49		53	Found 474, 476 (MH ⁺). C ₂₃ H ₂₄ BrNO ₅ . requires 473, 475

Description 50 (RS)-(1-{5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl}-methanoyl)-piperidin-2-yl)-acetic acid 2-phenyl-2-oxo-ethyl ester

The title compound (0.89g) was prepared from the acid of description 35 (0.72g) and 2-

5 bromoacetophenone (0.39g) by boiling in water/ethanol (15ml, 1:2) containing sodium carbonate (0.10g) for 4h, cooling removing solvent at reduced pressure and partitioning the residue between dichloromethane and water. The organic phase was separated, dried (MgSO₄) and solvent removed at reduced pressure.

Mass Spectrum (API⁺): Found 481 (MH⁺). C₂₆H₂₅FN₂O₄S requires 480

10

Description 51 (RS)-(4-{5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl}-methanoyl)-morpholin-3-yl)-acetic acid ethyl ester

Morpholin-3-ylacetic acid ethyl ester *Chem Pharm Bull* 94, 31(1), 1983 (2.10g) was dissolved in dichloromethane (50ml) and treated with triethylamine (1.33g). The mixture was cooled (ice

15

bath) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carbonyl chloride (1.53g) in dichloromethane (10ml) added. The mixture was stirred for 16h, diluted with water and the organic phase separated. The aqueous phase was extracted with dichloromethane (2 x 100ml), the organic phases combined, dried (Na₂SO₄) and solvent removed at reduced pressure. the residue was

column chromatographed (silica gel, 40% ethyl acetate:pentane → 60% ethyl acetate pentane eluant) to give the title compound (1.46g).

Mass Spectrum (API⁺): Found 393 (MH⁺). C₁₉H₂₁FN₂O₄S requires 392.

5 **Description 52 (RS)-(4-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-morpholin-3-yl)-acetic acid**

The title compound (1.33g) was prepared from the compound of description 51 (1.46), according to the method of description 35.

Mass Spectrum (API): Found 363 [(M - H)]. C₁₇H₁₇FN₂O₄S requires 364.

10 **Description 53 (RS)-(4-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-morpholin-3-yl)-acetic acid 2-oxo-2-phenyl-ethyl ester**

The title compound (0.57g) was prepared from the compound of description 52 (0.6g) and 2-bromoacetophenone (0.33g) according to the method of description 50.

15 Mass Spectrum (API⁺): Found 483 (MH⁺). C₂₅H₂₃FN₂O₅S requires 482.

Description 54 (RS)-2-{[2-(4-Fluoro-phenyl)-2-oxo-ethylcarbamoyl]-methyl}-piperidine-1-carboxylic acid *tert* butyl ester

The title compound (0.77g) was prepared from 2-carboxymethyl-piperidine-1-carboxylic acid *tert* butyl ester (0.80g) and 2-amino-1-(4-fluoro-phenyl)-ethanone (0.63g) according to the method of description 20.

Mass Spectrum (API⁺): Found 379 (MH⁺). C₂₁H₂₇FN₂O₄ requires 378.

Description 55 (RS)-2-[5-(4-Fluoro-phenyl)-oxazol-2-ylmethyl]-piperidine

25 The amide of description 54 (0.77g) and polyphosphoric acid (10h) were combined and heated together at 150°C for 4h. After cooling to room temperature the reaction mixture was poured onto ice/water and basified to pH 10 with potassium carbonate. The aqueous phase was extracted with dichloromethane, the combined extracts dried (MgSO₄) and solvent removed at reduced pressure to give the title compound (0.49g)

30 Mass Spectrum (API⁺): Found 261 (MH⁺). C₁₅H₁₇FN₂O requires 260.

Description 56 (RS)-2-{[2-phenyl-2-oxo-ethylcarbamoyl]-methyl}-piperidine-1-carboxylic acid *tert* butyl ester

The title compound (0.63g) was prepared from 2-carboxymethyl-piperidine-1-carboxylic acid *tert* butyl ester (0.50g) and 2-amino-1-phenylethanone (0.35g) according to the method of description 54.

35 Mass Spectrum (API⁺): Found 273 (MH⁺ - C₅H₉O₂). C₂₁H₂₈N₂O₄ requires 372.

Description 57 (RS)-2-(5-phenyloxazol-2-ylmethyl)-piperidine

40 The title compound (0.28g) was prepared from the amide of description 56 (0.40g) according to the method of description 55.

Mass Spectrum (API⁺): Found 243 (MH⁺). C₁₅H₁₈N₂O requires 242.

Description 58 (S)-2-[2-(4-Fluoro-phenyl)-2-oxo-ethoxycarbonylmethyl]-pyrrolidine-1-carboxylic *tert* butyl ester

The title compound (3.2g) was prepared from (S)-2-carboxymethyl-pyrrolidine-1-carboxylic acid *tert* butyl ester (2.02g) and 2-bromo-4'-fluoroacetophenone (1.91g) according to the method of description 36.

5 Mass Spectrum (API⁺): Found 266 (MH⁺ -C₅H₉O₂). C₁₉H₂₄FNO₅ requires 365 .

Description 59 (S)-2-[5-(4-Fluoro-phenyl)-1*H*-imidazol-2-ylmethyl]-pyrrolidine-1-carboxylic *tert* butyl ester.

10 The compound of description 58 (2.2g) was combined with ammonium acetate (8g) and warmed to 140°C for 1.5h. The reaction mixture was cooled, poured onto saturated potassium carbonate and extracted with dichloromethane (x 2). The combined dichloromethane extracts were dried (MgSO₄) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 20% ethyl acetate/pentane → ethyl acetate), the appropriate fractions were combined and solvent removed at reduced pressure to give the title compound (0.81g).

15 Mass Spectrum (API⁺): Found 346 (MH⁺). C₁₉H₂₄FN₃O₂ requires 345.

Description 60 5-(4-Fluoro-phenyl)-2-(S)-1-pyrrolidin-2-ylmethyl-1*H*-imidazole hydrochloride.

20 The compound of description 59 (0.80g) was dissolved in methanol (20ml) and treated with 4M HCl in dioxane (6ml). The mixture was stirred for 6h and then solvent removed at reduced pressure to give the title compound (0.57g) as a foam.

Mass Spectrum (API⁺): Found 346 (MH⁺). C₁₄H₁₅FN₃ requires 345.

25 **Description 61 (RS)-2-[2-(4-Fluoro-phenyl)-2-oxo-ethoxycarbonylmethyl]-piperidine-1-carboxylic *tert* butyl ester**

The title compound (3.83g) was prepared from (RS)-2-carboxymethyl-piperidine-1-carboxylic acid *tert* butyl ester (2.54g) and 2-bromo-4'-fluoroacetophenone (2.26g) according to the method of description 36.

30 Mass Spectrum (API⁺): Found 308 (MH⁺ -C₅H₉O₂). C₂₀H₂₆FNO₅ requires 307.

Description 62 (RS)-2-[5-(4-Fluoro-phenyl)-1*H*-imidazol-2-ylmethyl]-piperidine-1-carboxylic *tert* butyl ester.

The title compound (0.80g) was prepared from the compound of description 61 (1.40g) according to the method of example 59.

35 Mass Spectrum (API⁺): Found 360 (MH⁺). C₂₀H₂₆FN₃O₂ requires 359.

Description 63 5-(4-Fluoro-phenyl)-2-(RS)-1-piperidine-2-ylmethyl-1*H*-imidazole hydrochloride.

40 The title compound (0.65g) was prepared from the compound of description 62 (0.70g) according to the method of description 60.

Mass Spectrum (API⁺): Found 346 (MH⁺). C₁₅H₁₇FN₃ requires 345.

Description 64 (RS)-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-acetic acid 2-(2-bromophenyl)-2-oxo-ethyl ester

The title compound (0.51g) was prepared from the acid of description 35 (0.60g) and 2-bromo-2'-bromoacetophenone (0.51g) according to the method of description 36.

5 Mass Spectrum (API⁺): Found 559, 561 (MH⁺). C₂₆H₂₄BrF₂N₂O₄S requires 558, 560

Description 65 (RS)-2-[2-(4-Fluoro-phenyl)-2-oxo-ethoxycarbonylmethyl]-piperidine-1-carboxylic acid *tert* butyl ester

10 The title compound (3.70g) was prepared from (RS)2-carboxymethyl-piperidine-1-carboxylic acid *tert* butyl ester (2.50g) according to the method of example 36

Mass Spectrum (API⁺): Found 380 (MH⁺). C₂₀H₂₆FNO₅ requires 379

Description 66 (RS)-2-[5-(4-Fluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidine-1-carboxylic acid *tert* butyl ester

15 The title compound (1.71g) was prepared from the compound of description 65 (3.70g) according to the method of description 59.

Mass Spectrum (API⁺): Found 366 (MH⁺). C₂₀H₂₆FN₃O₂ requires 365

Description 67 (RS)-2-[4-Bromo-5-(4-fluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidine-1-carboxylic acid *tert* butyl ester

20 The compound of description 66 (0.62g) was dissolved in DMF (2ml) containing potassium bicarbonate (0.29g) and the mixture cooled (ice/salt bath). Bromine (0.15ml) was added, the mixture stirred for 15 min, poured onto crushed ice and 20% ammonia added to destroy excess bromine. The mixture was extracted with diethyl ether (x 3), the combined organic phase washed with water (x 3, dried (MgSO₄) and solvent removed at reduced pressure to give after chromatography (silica gel, 0 → 20% ethyl acetate/pentane eluant), the title compound as a gum (0.25g)

25 Mass Spectrum (API⁺): Found 438, 440 (MH⁺). C₂₀H₂₅BrFN₃O₂ requires 437, 439

Description 68 (RS)-2-[4-Bromo-5-(4-fluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidine hydrochloride

30 The title compound (0.27g) was prepared from the compound of description 67 (0.25g) according to the procedure of description 60.

35 Mass Spectrum (API⁺): Found 338, 340 (MH⁺). C₁₅H₁₇BrFN₃ requires 337, 339

Description 69 (RS)-(1-{1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-yl)-acetic acid 2-(4-fluoro-phenyl)-2-oxo-ethyl ester

40 The title compound (0.74g) was prepared from piperidin-2-yl-acetic acid methyl ester (0.36g) and {1-[4-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]carboxylic acid (0.5g) according to the method of descriptions 34, 35 and 36.

Description 70 (RS)(1-{1-[4-(4-Fluoro-phenyl)-1H-pyrazol-3-yl]-methanoyl}-piperidin-2-yl)-acetic acid 2-(4-fluoro-phenyl)-2-oxo-ethyl ester

The title compound (0.51g) was prepared from piperidin-2-yl-acetic acid methyl ester (0.38g) and {1-[4-(4-Fluoro-phenyl)-1H-pyrazol-3-yl]carboxylic acid (0.5g) according to the method of descriptions 34, 35 and 36.

5 **Description 71 (RS)-[1-(1-Quinolin-2-yl-methanoyl)-piperidin-2-yl]-acetic acid 2-(4-fluoro-phenyl)-2-oxo-ethyl ester**

The title compound (0.48g) was prepared from piperidin-2-yl-acetic acid methyl ester (0.38g) and quinoline-2-carboxylic acid (0.5g) according to the method of descriptions 34, 35 and 36.

10 **Description 72 (RS)-2-[2-phenyl-2-oxo-ethoxycarbonylmethyl]-piperidine-1-carboxylic tert butyl ester**

The title compound (7.07g) was prepared from (RS)-2-carboxymethyl-piperidine-1-carboxylic acid tert butyl ester (5.0g) and 2-bromoacetophenone (4.18g) according to the method of description 36. Mass Spectrum (API⁺): Found 262 (MH⁺ -C₅H₉O₂). C₂₀H₂₇NO₅ requires 361.

15

Description 73 (RS)-2-[5-Phenyl-1H-imidazol-2-ylmethyl]-piperidine-1-carboxylic tert butyl ester.

The title compound (3.78g) was prepared from the compound of description 72 (7.07g) according to the method of example 59.

20

Mass Spectrum (API⁺): Found 242 (MH⁺ -C₅H₉O₂). C₂₀H₂₇N₃O₂ requires 341.

Description 74 5-Phenyl-2-(RS)-1-piperidine-2-ylmethyl-1H-imidazole .

The title compound (0.65g) was prepared from the compound of description 73 (0.70g) according to the method of description 60. The hydrochloride salt generated during the reaction was neutralised by dissolving the product in water, neutralising with solid potassium carbonate, extracting with dichloromethane, drying the organic phase (Na₂SO₄) and removing the solvent at reduced pressure. Mass Spectrum (API⁺): Found 242 (MH⁺). C₁₅H₁₈N₃ requires 241.

25

Description 75 (RS)-2-(2-Oxo-2-phenyl-ethoxycarbonylmethyl)-piperidine-1-carboxylic acid benzyl ester

The title compound (4.0g) was prepared from 2-bromoacetophenone (2.20g) and 2-carboxymethyl-piperidine-1-carboxylic acid benzyl ester according to the method of description 36

Mass Spectrum (API⁺): Found 396 (MH⁺). C₂₃H₂₅NO₅ requires 395.

30

Description 76 (RS)-2-(4-Phenyl-oxazol-2-ylmethyl)-piperidine-1-carboxylic acid benzyl ester

The title compound (0.95g) was prepared from the compound of description 75 (3.0g) according to the method of Example 54.

Mass Spectrum (API⁺): Found 377 (MH⁺). C₂₃H₂₄N₂O₃ requires 376.

35

Description 77 (RS)-2-(4-Phenyl-oxazol-2-ylmethyl)-piperidine

The compound of description 76 (0.097g) and 10% palladium/charcoal (0.05g) in ethanol (5ml) containing cyclohexene (0.5ml) was heated at 75°C for 1.5h, cooled, filtered (kieselguhr) and solvent removed at reduced pressure to give the title compound (0.06g).

Mass Spectrum (API⁺): Found 243 (MH⁺). C₁₅H₁₈N₂O requires 242.

5

Description 78 (RS)-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-acetic acid hydrazide

The ester of description 34 (1.06g) in ethanol (25ml) was treated with hydrazine hydrate (5ml) and the mixture boiled for 24h. Solvent was removed at reduced pressure and the residue column

10 chromatographed (silica gel; 0 → 10% methanol/dichloromethane). The appropriate fractions were combined and solvent removed at reduced pressure to give the title compound (0.62g).

Mass Spectrum (API⁺): Found 377 (MH⁺). C₁₈H₂₁N₄O₂S requires 376.

Description 79 (RS)-2-Hydrazinocarbonylmethyl-piperidine-1-carboxylic acid tert butyl ester

15 The title compound (2.98g) was prepared from 2-methoxycarbonylmethyl-piperidine-1-carboxylic acid tert butyl ester (3.08g) according to the method of description 78.

Mass Spectrum (API⁺): Found 258 (MH⁺). C₁₂H₂₃N₃O₃ requires 257.

Description 80 (RS)-2-[5-(4-Fluoro-phenyl)-4H-[1,2,4]triazol-3-ylmethyl]-piperidine-1-carboxylic acid tert butyl ester.

20 The title compound (0.32g) was prepared from the compound of description 79 (1.49g) according to the method of example 105.

Mass Spectrum (API⁺): Found 361 (MH⁺). C₁₉H₂₅FN₄O₂ requires 360.

Description 81 (RS)-2-[5-(4-Fluoro-phenyl)-4H-[1,2,4]triazol-3-ylmethyl]-piperidine

25 The title compound (0.31g) was prepared from the compound of description 80 (.32g) according to the method of description 2.

Mass Spectrum (API⁺): Found 261 (MH⁺). C₁₄H₁₇FN₄ requires 260.

Description 82 (RS)-2-[2-(3-Methoxy-phenyl)-2-oxo-ethoxycarbonylmethyl]-piperidine-1-carboxylic tert butyl ester

30 The title compound (3.06g) was prepared from (RS)-2-carboxymethyl-piperidine-1-carboxylic acid tert butyl ester (2.0g) and 2-bromo-3'-methoxyacetophenone (1.88g) according to the method of description 36.

35 Mass Spectrum (API⁺): Found 292 (MH⁺ -C₅H₈O₂). C₂₁H₂₉NO₆ requires 391.

Description 83 (RS)-2-[5-(3-Methoxy-phenyl)-1H-imidazol-2-ylmethyl]-piperidine-1-carboxylic tert butyl ester.

40 The title compound (3.78g) was prepared from the compound of description 82 (3.0g) according to the method of description 59.

Mass Spectrum (API⁺): Found 272 (MH⁺ -C₅H₉O₂) C₂₁H₂₉N₃O₃ requires 371.

Description 84 5-(3-Methoxy-phenyl)-2-(RS)-1-piperidine-2-ylmethyl-1H-imidazole .

The title compound (1.06g) was prepared from the compound of description 83 (1.33g) according to the method of description 2.

Mass Spectrum (API⁺): Found 242 (MH⁺). C₁₅H₁₈N₃ requires 241.

5 **Description 85 (RS)-2-[2-(3-Chloro-phenyl)-2-oxo-ethoxycarbonylmethyl]-piperidine-1-carboxylic tert butyl ester**

The title compound (2.65g) was prepared from (RS)-2-carboxymethyl-piperidine-1-carboxylic acid tert butyl ester (2.0g) and 2-bromo-3'-chloroacetophenone (1.92g) according to the method of description 36.

10 Mass Spectrum (API⁺): Found 396, 398 (MH⁺). C₂₀H₂₆NO₅Cl requires 395, 397.

Description 86 (RS)-2-[5-(3-Chloro-phenyl)-1H-imidazol-2-ylmethyl]-piperidine-1-carboxylic tert butyl ester.

The title compound (1.61g) was prepared from the compound of description 85 (2.65g) according to the method of description 59.

15 Mass Spectrum (API⁺): Found 375, 377 (MH⁺). C₂₀H₂₅ClN₃O₂ requires 374, 376.

Description 87 5-(3-Chloro-phenyl)-2-(RS)-1-piperidine-2-ylmethyl-1H-imidazole .

The title compound (0.85g) was prepared from the compound of description 86 (1.05g) according to the method of description 2.

20 Mass Spectrum (API⁺): Found 275, 277 (MH⁺). C₁₅H₁₇ClN₃ requires 274, 276.

Description 88 (RS)-2-[2-(3-Cyano-phenyl)-2-oxo-ethoxycarbonylmethyl]-piperidine-1-carboxylic tert butyl ester

25 The title compound (1.51g) was prepared from (RS)-2-carboxymethyl-piperidine-1-carboxylic acid tert butyl ester (1.15g) and 2-bromo-3'-cyanoacetophenone (1.06g) according to the method of description 36.

Mass Spectrum (API⁺): Found 387 (MH⁺). C₂₁H₂₆N₂O₅ requires 386.

30 **Description 89 (RS)-2-[5-(3-Cyano-phenyl)-1H-imidazol-2-ylmethyl]-piperidine-1-carboxylic tert butyl ester.**

The title compound (1.25g) was prepared from the compound of description 88 (1.50g) according to the method of description 59.

Mass Spectrum (API⁺): Found 366 (MH⁺). C₂₁H₂₅N₄O₂ requires 365.

35 **Description 90 5-(3-Cyano-phenyl)-2-(RS)-1-piperidine-2-ylmethyl-1H-imidazole .**

The title compound (0.85g) was prepared from the compound of description 89 (1.25g) according to the method of description 2.

Mass Spectrum (API⁺): Found 266 (MH⁺). C₁₆H₁₇N₄ requires 265.

40

Description 91 (RS)-1-Benzyl-2-[5-(4-fluoro-phenyl)-tetrazol-2-ylmethyl]-piperidine

N-Benzyl-2-bromomethylpiperidine (2.1g), 5-(4-fluoro-phenyl)-2H-tetrazole (1.28g) and potassium carbonate (6g) were combined in xylene (100ml) containing diisopropylethylamine (7ml) and boiled for 16h. The reaction mixture was cooled to room temperature, filtered, solvent removed at reduced pressure and the residue column chromatographed (silica gel; diethyl ether/petroleum ether 40:60 eluant) to give after combining appropriate fractions and removing solvent at reduced pressure the title compound 1.44g.

5 Mass Spectrum (API⁺): Found 340 (MH⁺). C₁₉H₂₂N₅F requires 339.

Description 92 (RS)-2-[5-(4-Fluoro-phenyl)-tetrazol-2-ylmethyl]-piperidine

10 The compound of description 91 (1.4g) was dissolved in ethanol (100ml), palladium hydroxide (0.40g) added and the mixture hydrogenated at 50 psi and 50°C for 3h. The mixture was filtered through kieselguhr and solvent removed at reduced pressure and the residue triturated with diethyl ether/petroleum ether to give the title compound as a solid.

15 Mass Spectrum (API⁺): Found 250 (MH⁺). C₁₂H₁₆N₅F requires 249.

Description 93 (RS)-1-Benzyl-2-(4-phenyl-imidazol-1-ylmethyl)-piperidine

4-Phenylimidazole (1.3g) was treated with sodium hydride (0.6g 50% in oil) in dry tetrahydrofuran (80ml). When gas evolution had ceased, 2-bromomethyl-N-benzylpiperidine (2.5g) in tetrahydrofuran (30ml) was added. The mixture was stirred for 16h, solvent removed at reduced pressure and treated with ice/water (1:1, 100ml). The mixture was extracted with dichloromethane (2x), the combined organic phase washed with water, solvent removed at reduced pressure and the residue column chromatographed (silica gel, 0.5 → 9.5% dichloromethane / methanol). Appropriate fractions were combined to give the title compound 0.72g.

20 Mass Spectrum (API⁺): Found 332 (MH⁺). C₂₂H₂₅N₃ requires 331.

Description 94 (RS)-2-(4-Phenyl-imidazol-1-ylmethyl)-piperidine

25 The title compound (0.50g) was prepared from the compound of description 93 (0.70g) according to the method of description 92.

Mass Spectrum (API⁺): Found 241 (MH⁺). C₁₅H₁₉N₃ requires 241.

Description 95 (RS)-1-Benzyl-2-[3-(4-fluoro-phenyl)-pyrazol-1-ylmethyl]-piperidine

30 The title compound (0.8g) was prepared from 2-bromomethyl-N-benzylpiperidine (2.68g) and 3-(4-fluoro-phenyl)-1H-pyrazole (1.62g) according to the method of example 93.

Mass Spectrum (API⁺): Found 350 (MH⁺). C₂₂H₂₄FN₃ requires 349.

Description 96 (RS)-2-[3-(4-Fluoro-phenyl)-pyrazol-1-ylmethyl]-piperidine

35 The title compound (0.5g) was prepared form the compound of description 95 (0.8g) according to the method of description 94.

Mass Spectrum (API⁺): Found 260 (MH⁺). C₁₅H₁₈FN₃ requires 259.

Description 97 (RS)-2-Carbamoylmethyl-piperidine-1-carboxylic acid tert butyl ester.

40 The title compound (0.92g) was prepared from 2-(RS)-carboxymethyl-piperidine-1-carboxylic acid tert butyl ester (2.0g) and ammonium chloride (0.86g) according to the method of Example 97.

Mass Spectrum (API⁺): Found 143 (MH⁺ - C₅H₈O₂). C₁₂H₂₂N₂O₃ requires 242.

Description 98 (RS)-2-Thiocarbamoylmethyl-piperidine-1-carboxylic acid tert butyl ester

The compound of description 97 (0.90g) and Lawesson's reagent (0.90g) were combined in dry

5 toluene (30ml) and heated at 100°C (oil bath temperature) for 6h. Solvent was removed at reduced pressure and the residue column chromatographed (silica gel; dichloromethane eluant) to give after combining appropriate fractions the title compound (0.82g) after trituration with petroleum ether/diethyl ether.

Mass Spectrum (API⁺): Found 159 (MH⁺ - C₅H₈O₂). C₁₂H₂₂N₂O₂S requires 258.

10

Description 99 (RS)-2-(4-Phenyl-thiazol-2-ylmethyl)-piperidine

The compound of description 98 (0.67g) and 2-bromoacetophenone (0.52g) were combined in ethanol (20ml), stirred at room temperature for 8h and then boiled for 48h. Solvent was removed at reduced pressure and the residue column chromatographed (silica gel; ethyl acetate/n-pentane → 1%

15

ammonia/methanol /dichloromethane) to give the title compound (0.21g)

Mass Spectrum (API⁺): Found 259 (MH⁺). C₁₅H₁₈N₂S requires 258.

Description 100 (RS)-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-acetic acid hydrazide

20

The title compound (0.24g) was prepared from (1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-acetic acid methyl ester (0.25g) according to the method of description 17.

Mass Spectrum (API⁺): Found 377 (MH⁺). C₁₈H₂₁N₄O₂FS requires 376.

25

Description 101 (RS)-2,5-Dimethyl-2H-pyrazole-3-carboxylic acid N'-[2-(1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-ethanoyl]-hydrazide

The title compound (0.36g) was prepared from the compound of description 100 (0.23g) and 1,3-dimethylpyrazole-5-carboxylic acid according to the method of description 20.

Mass Spectrum (API⁺): Found 497 (MH⁺). C₂₄H₂₇N₆O₃FS requires 498.

30

Description 102 (RS)-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-acetic acid 2-oxo-1,2-diphenyl-ethyl

The title compound (0.54g) was prepared from the compound of description 35 (0.40g) and desyl bromide (0.30g) according to the method of example 36

35

Mass Spectrum (API⁺): Found 557 (MH⁺). C₃₂H₂₉FN₂O₄S requires 556.

Description 103 (RS)-2-[N'-(1-Benzofuran-2-yl-methanoyl)-hydrazino]-2-oxo-ethyl]-piperidine-1-carboxylic acid tert butyl ester

The title compound (2.4g) was prepared from the compound of description 17 and benzofuran-2-carboxylic acid according to the method of description 20.

Mass Spectrum (API⁺): Found 402 (MH⁺). C₂₁H₂₇N₃O₅ requires 401.

Description 104 (RS)-2-(5-Benzofuran-2-yl-[1,3,4]oxadiazol-2-ylmethyl)-piperidine

The title compound (0.77g) was prepared from the compound of description 103 according to the method of description 19.

Mass Spectrum (API⁺): Found 284 (MH⁺). C₁₆H₁₇N₃O₂ requires 283.

5 **Description 105 (RS)-2-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-acetamide**

The compound of description 34 (0.87g) and formamide (0.3ml) were combined in tetrahydrofuran and boiled while adding 3 portions of sodium methoxide (0.12ml each addition, 20% in methanol) over 20min. After the final addition the reaction was heated for a further 6h at reflux. The reaction was cooled to room temperature diluted with dichloromethane and water and the aqueous phase separated. The organic phase was washed with water dried (MgSO₄) and solvent removed at reduced pressure to give the title compound (1.40g)

Mass Spectrum (API⁺): Found 362 (MH⁺). C₁₈H₂₀FN₃O₂S requires 361.

15 **Description 106 (RS)-(1-{1-[5-(3,4-Difluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-acetic acid 2-(4-fluoro-phenyl)-2-oxo-ethyl ester**

The title compound (0.435g) was prepared from the compound of description 35 (0.40g) and 2-bromo-3',4'-difluoroacetophenone (0.26g) according to the method of description 36.

Mass Spectrum (API⁺): Found 517 (MH⁺). C₂₄H₂₃F₃N₂O₄S requires 516.

20 **Description 107 (RS)-(1-{1-[5-(3-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-acetic acid 2-(4-fluoro-phenyl)-2-oxo-ethyl ester**

The title compound (0.430g) was prepared from the compound of description 35 (0.40g) and 2-bromo-3'-fluoroacetophenone (0.240g) according to the method of description 36

25 Mass Spectrum (API⁺): Found 499 (MH⁺). C₂₄H₂₄F₂N₂O₄S requires 498.

Description 108. (RS)-1-(4-Fluorophenyl)-4-(1-{1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]-methanoyl}-piperidin-2-yl)-butane-1,3-dione

A. (1-{1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]-methanoyl}-piperidin-2-yl)-acetic acid

30 (0.500g) was dissolved in dry tetrahydrofuran (15ml) and cooled to -20°C under an atmosphere of argon. Triethylamine (0.231ml) and isobutylchloroformate (0.215ml) were added and the solution was stirred at -20°C for 1 hour. The solution was then cooled to -78°C.

B. A solution of 4'-fluoroacetophenone (0.229g) in THF (15ml) was cooled to

35 -20°C under an atmosphere of argon. A solution of lithium diisopropylamide (0.830ml; 2M solution in THF) was added and stirring continued at -20°C for 30 minutes. The solution was then cooled to -78°C.

C. The solution from part B was added to the stirred solution of part A by way of a cannula.

40 Stirring was continued at -78°C under an atmosphere of argon for 2 hours before being quenched by the addition of saturated ammonium chloride solution. After reaching room temperature, the reaction solution was partitioned between ethyl acetate and water. The organic solution was washed with brine, dried (MgSO₄) and evaporated. The residue was chromatographed over silica

gel, eluting with a gradient of 10 to 75% ethyl acetate in hexane. The title compound was obtained as a colourless oil (0.560g) mass spectrum (API⁺) 483 [MH⁺], (API⁻) 481 [(M-H)⁻] C₂₆H₂₄F₂N₂O₃S requires 482.

5 **Description 109. (RS)-2-Carboxymethylpiperazine-1,4-dicarboxylic acid 4-tert-butyl ester 1-(9H-fluoren-9-ylmethyl) ester**
 3-Methoxycarbonylmethylpiperazine-1-carboxylic acid tert-butyl ester (6.0g) was dissolved in THF (60ml) and 1N sodium hydroxide solution (60ml) and stirred at room temperature for 6 hours. The solution was then cooled to 5°C and adjusted to pH 9 - 10 by the addition of 10% hydrochloric acid. Na(9-Fluorenylmethoxycarbonyl chloride (6.05g) was then added 10 portionwise, maintaining the pH at 9 - 10 by the addition of 1N NaOH solution. The reaction mixture was stirred at 5°C for 16 hours. The solution was then adjusted to pH 1 by the addition of 10% hydrochloric acid. The solution was extracted with ethyl acetate (x2), dried (MgSO₄) and evaporated. The title compound was obtained as a white foam (9.96g), mass spectrum (API⁺) 411 [(M-C₄H₈)H⁺], C₂₆H₃₀N₂O₆ requires 466.

Description 110 (RS)-3-[2-(4-Fluorophenyl)-2-oxo-ethoxycarbonylmethyl]piperazine-1-carboxylic acid tert-butyl ester

20 (RS)-2-Carboxymethylpiperazine-1,4-dicarboxylic acid 4-tert-butyl ester 1-(9H-fluoren-9-ylmethyl) ester from description 109 (2.0g) was dissolved in DMF (25ml) and stirred at room temperature under argon for 3 days in the presence of potassium carbonate (0.697g) and 2-bromo-4'-fluoroacetophenone (0.930g). The reaction solution was then partitioned between ethyl acetate and water. the organic solution was washed with brine, dried (MgSO₄) and evaporated. The 25 crude product was chromatographed over silica gel, eluting with 25 to 100% ethyl acetate in hexane, followed by 10% ethanol in ethyl acetate. The title compound was obtained as a pale yellow solid (0.887g), mass spectrum (API⁺) 381 [MH⁺], C₁₉H₂₅FN₂O₅ requires 380.

Description 111. (RS)-4-{1-[5-(4-Fluorophenyl)-2-methylthiazol-4-yl]-methanoyl}-3-[2-(4-fluoro-phenyl)-2-oxo-ethoxycarbonylmethyl]-piperazine-1-carboxylic acid tert-butyl ester

30 (RS)-3-[2-(4-Fluorophenyl)-2-oxo-ethoxycarbonylmethyl]-piperazine-1-carboxylic acid tert-butyl ester description 110 (0.887g) was reacted with HATU (0.932g), diisopropylethylamine (1.30ml) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.707g) in dry DMF (8ml) according to the method of description 20. Silica gel column chromatography, eluting with ethyl 35 acetate-hexane mixtures provided the title compound as a white foam (1.168g), mass spectrum (API⁺) 600 [MH⁺], C₃₀H₃₁F₂N₃O₆S requires 599.

Description 112. (RS)-3-[4-(4-Fluorophenyl)-1H-imidazol-2-ylmethyl]-4-{1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]-methanoyl}-piperazine-1-carboxylic acid tert-butyl ester

40 (RS)-4-{1-[5-(4-Fluorophenyl)-2-methylthiazol-4-yl]-methanoyl}-3-[2-(4-fluoro-phenyl)-2-oxo-ethoxycarbonylmethyl]-piperazine-1-carboxylic acid tert-butyl ester from description 111 (0.360g) and anhydrous ammonium acetate were heated to 140 °C under argon for 1.5 hours with stirring. After cooling, the reaction mixture was partitioned between dichloromethane and

saturated potassium carbonate solution. The organic solution was washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed over silica gel, eluting with 0 to 10% ethanol in ethyl acetate. The title compound was obtained as a white foam (0.125g), mass spectrum (API^+) 580 [MH^+], $C_{30}H_{31}F_2N_5O_3S$ requires 579.

5

Description 113. (RS)-4-{1-[5-(4-Fluorophenyl)-2-methylthiazol-4-yl]-methanoyl}-3-[4-(4-fluoro-phenyl)-oxazol-2-ylmethyl]-piperazine-1-carboxylic acid *tert*-butyl ester
 (RS)-4-{1-[5-(4-Fluorophenyl)-2-methylthiazol-4-yl]-methanoyl}-3-[2-(4-fluoro-phenyl)-2-oxo-ethoxycarbonylmethyl]-piperazine-1-carboxylic acid *tert*-butyl ester, description 111 (0.385g), $tert$ -butyl carbamate (0.376g) and boron trifluoride etherate (4 drops) were dissolved in xylene (5ml) and heated to 140°C, under argon and with stirring for 48 hours. After cooling, the reaction mixture was partitioned between ethyl acetate and saturated sodium hydrogen carbonate solution. The organic layer was dried ($MgSO_4$), evaporated and the residue chromatographed over silica gel. Elution with a gradient of 25 to 100% ethyl acetate in hexane provided the title compound as a pale yellow oil (0.130g), mass spectrum (API^+) 581 [MH^+], $C_{30}H_{30}F_2N_4O_4S$ requires 580.

10

15 **Description 114. (S)-2-Methoxycarbonylmethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester**
 A solution of (S)-2-carboxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (2.00g) in methanol (1.32ml)/ acetonitrile (40ml) was treated with *N,N*-diisopropylethylamine (1.78ml). Trimethylsilyldiazomethane (2M, 8.73ml) was added dropwise and the resulting mixture was stirred at room temperature, under argon for 24h. The mixture was diluted with ethyl acetate, washed with 2M HCl, saturated aqueous sodium hydrodgen carbonate, brine then dried (magnesium sulfate). The solvent was removed under reduced pressure to afford the title compound (2.10g)

20

25 Mass Spectrum (API^+): 144 ($MH^+ \cdot BOC$). $C_{12}H_{21}NO_4$ requires 243.

Description 115. (S)-2-Hydrazinocarbonylmethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester

30

The ester of description 114 (2.10g) was treated with hydrazine hydrate (16.3ml) as described in description 78 to afford the title compound (1.60g).

Mass Spectrum (API^+): 144 ($MH^+ \cdot BOC$). $C_{11}H_{21}N_3O_3$ requires 243.

35

Description 116. (S)-2-(5-Phenyl-4*H*-[1,2,4]triazol-3-ylmethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

Benzamidine hydrochloride (0.84g) in ethanol (20ml) was treated with 25% sodium methoxide solution in methanol (2.44ml) and stirred for 45min. at room temperature under argon. The hydrazide of description 115 (1.3g) was added and the mixture was heated at reflux for 24h. After cooling the solvent was removed under reduced pressure then the residue was partitioned between

40

dichloromethane and water. The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was column chromatographed (silica gel; 0→50% ethyl acetate-pentane) to afford the title compound (0.26g).

Mass Spectrum (API^+): 329 (MH^+). $C_{18}H_{24}N_4O_2$ requires 328.

Description 117. 3-Phenyl-5-(S)-1-pyrrolidin-2-ylmethyl-4H-[1,2,4]triazole

The compound of description 116 (0.13g) was treated with trifluoroacetic acid (2.5ml) according to a method similar to that of description 2 to afford the title compound (0.09g).

5 Mass Spectrum (API⁺): 229 (MH⁺). C₁₃H₁₆N₄ requires 228.

Description 118. (S)-2-(2-Oxo-2-phenyl-ethoxycarbonylmethyl)-pyrrolidine-1-carboxylic acid benzyl ester

The title compound (0.700g) was prepared from (S)-2-carboxymethyl-pyrrolidine-1-carboxylic acid

10 benzyl ester (1.00g, Aoyama et al, Chem. Pharm. Bull., 3249, 29,11,1981) and 2-bromoacetophenone (0.760g) according to the method of description 36.

Mass Spectrum (API⁺): 382 (MH⁺). C₂₂H₂₃NO₅ requires 381.

Description 119. (S)-2-(4-Phenyl-oxazol-2-ylmethyl)-pyrrolidine-1-carboxylic acid benzyl ester

15 The title compound (0.290g) was prepared from the compound of description 118 (0.700g) according to the method of example 54 using xylene as solvent.

Mass Spectrum (API⁺): 363 (MH⁺). C₂₂H₂₂N₂O₃ requires 362.

Description 120. 4-Phenyl-2-(S)-1-pyrrolidin-2-ylmethyl-oxazole

20 The title compound (0.065g) was prepared by treating the compound of description 119 (0.280g) with 10% palladium/charcoal (0.150g, 50% paste) according to the method of description 77.

The product was purified by column chromatography (silica gel, 0→4% (10% .880 ammonia-methanol)-dichloromethane).

Mass Spectrum (API⁺): 229 (MH⁺). C₁₄H₁₆N₂O requires 228.

25

Description 121. (RS)-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-yl)-acetic acid 2-(2-bromo-phenyl)-2-oxo-ethyl ester

The title compound (3.0g) was prepared as a brown oil from the acid of description 35 (2.5g) and (2-bromo-phenyl)-acetyl bromide (1.92g) according to the method of description 36.

30 Mass Spectrum (API⁺): Found 559,561 (MH⁺). C₂₆H₂₄BrFN₂O₄S requires 558,560.

Description 122. (RS)-2-[4-(2-Fluoro-phenyl)-thiazol-2-ylmethyl]-piperidine

The title compound (0.335g) was prepared as an oil from the compound of description 98 (0.750g) and 2-bromo-1-(2-fluoro-phenyl)-ethanone (0.631g) according to the method of description 99.

35 Mass Spectrum (API⁺): Found 277. (MH⁺). C₁₅H₁₇FN₂S requires 276.

Description 123. (RS)-2-[4-(3-Fluoro-phenyl)-thiazol-2-ylmethyl]-piperidine

The title compound (0.310g) was prepared as an oil from the compound of description 98 (0.750g) and 2-bromo-1-(3-fluoro-phenyl)-ethanone (0.631g) according to the method of description 99.

40 Mass Spectrum (API⁺): Found 277. (MH⁺). C₁₅H₁₇FN₂S requires 276.

Example 1 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-methanone

2-Methyl-5-(4-fluorophenyl)-thiazole-4-carboxylic acid (0.07g), [O-(7-azabenzotriazol-1-yl)-

5 1,1,3,3-tetramethyluronium hexafluorophosphate] (0.12g) and diisopropylaelethylamine (0.17ml) in dimethylformamide (5ml) was stirred for 15 min. The amine of D2 (0.075g) was added and the mixture stirred for 16h. Solvent was removed at reduced pressure, the residue dissolved in ethyl acetate and washed with water. The organic phase was separated dried (MgSO_4) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 0 – 100% ethyl acetate/pentane) to give the title compound (0.095g).

10 Mass Spectrum (API⁺): Found 463 (MH^+). $\text{C}_{25}\text{H}_{23}\text{FN}_4\text{O}_2\text{S}$ requires 462.

Example 2 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-2H-[1,2,3]triazol-4-yl]-1-[2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-methanone.

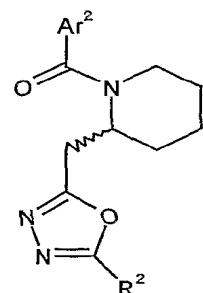
15 A mixture of 5-(4-Fluoro-phenyl)-2-methyl-2H-[1,2,3]triazole-4-carbonyl chloride (0.115g) and the amine D2 were combined in dichloromethane (10ml) containing triethylamine (0.2ml). The mixture was stirred for 16h, washed with water, the organic phase dried (MgSO_4) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 40 – 60% ethyl acetate/pentane eluant) to give the title compound (0.154g).

20 Mass Spectrum (API⁺): Found 447 (MH^+). $\text{C}_{24}\text{H}_{23}\text{FN}_6\text{O}_2$ requires 446.

The compounds of the examples of Table 1 were prepared by analogous procedures to those used to prepare the compounds of Example 1 and Example 2 from the corresponding amine and carboxylic acid (Method 1) or from the corresponding amine and acid chloride (Method 2).

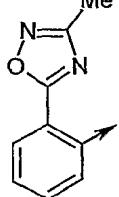
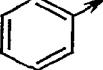
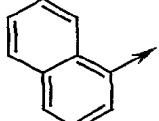
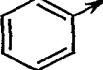
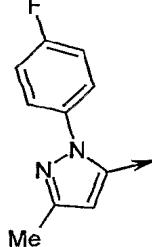
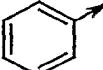
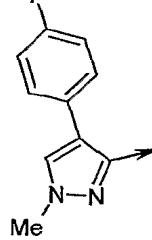
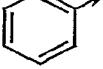
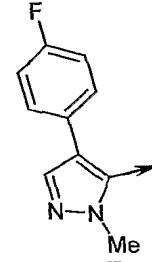
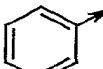
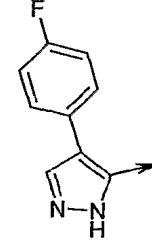
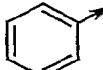
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Table 1: 5-Aryl-[1,3,4]oxadiazol-2-ylpiperidines

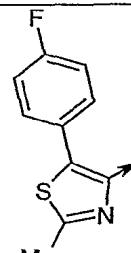
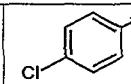
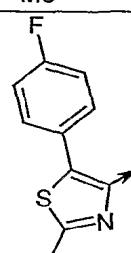
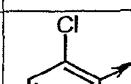
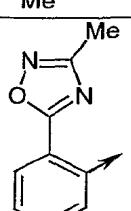
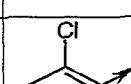
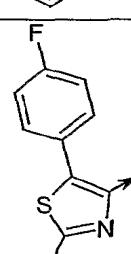
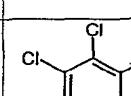
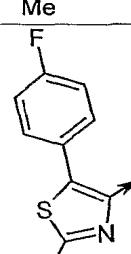
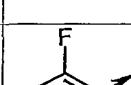
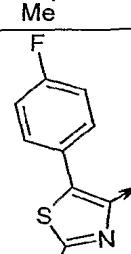
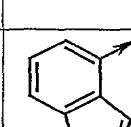


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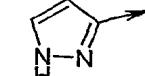
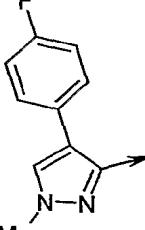
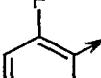
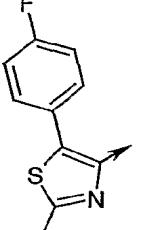
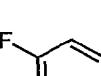
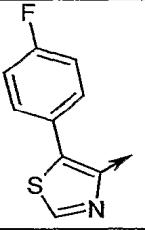
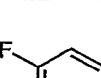
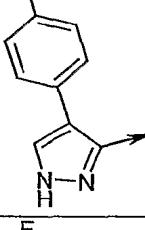
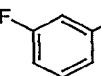
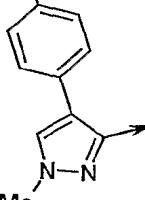
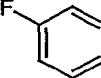
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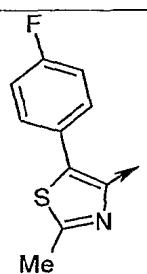
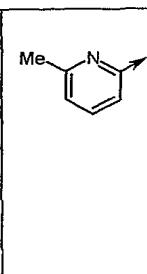
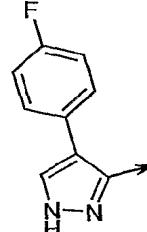
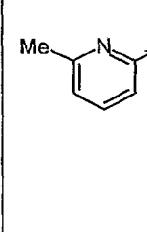
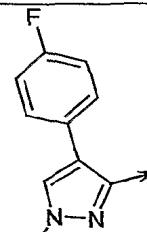
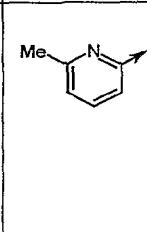
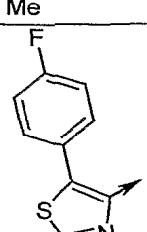
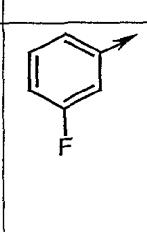
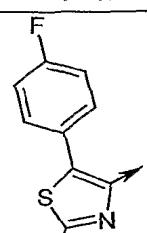
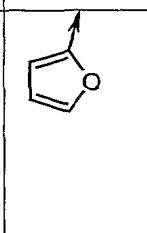
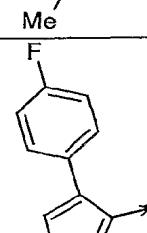
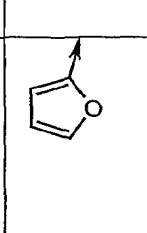
Example	Amine	Method	Ar ²	R ²	yield %	Mass Spectrum (Electrospray LC/MS)
3	D2	1			56	Found 430 (MH ⁺). C ₂₄ H ₂₃ N ₅ O ₃ . requires 429
4	D2	2			86	Found 398 (MH ⁺). C ₂₅ H ₂₃ N ₃ O ₂ . requires 397
5	D2	2			79	Found 446 (MH ⁺). C ₂₅ H ₂₄ FN ₅ O ₂ . requires 445
6	D2	2			64	Found 446 (MH ⁺). C ₂₅ H ₂₄ FN ₅ O ₂ . requires 445
7	D2	2			42	Found 446 (MH ⁺). C ₂₅ H ₂₄ FN ₅ O ₂ . requires 445
8	D2	2			53	Found 432 (MH ⁺). C ₂₄ H ₂₂ FN ₅ O ₂ . requires 431

9	D4	1			56	Found 448 (MH ⁺). C ₂₄ H ₂₂ FN ₅ O ₂ . requires 447
10	D4	1			77	Found 481 (MH ⁺). C ₂₅ H ₂₂ F ₂ N ₄ O ₂ S. requires 480
11	D6	1			54	Found 497, 499 (MH ⁺). C ₂₅ H ₂₂ ClFN ₄ O ₂ S. requires 496, 498
12	D6	1			57	Found 464, 466 (MH ⁺). C ₂₄ H ₂₂ ClN ₅ O ₃ . requires 463, 465
13	D8	1			59	Found 464 (MH ⁺). C ₂₄ H ₂₂ FN ₅ O ₂ S. requires 463
14	D10	1			64	Found 481 (MH ⁺). C ₂₅ H ₂₂ F ₂ N ₄ O ₂ S. requires 480

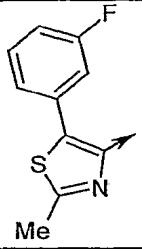
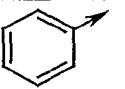
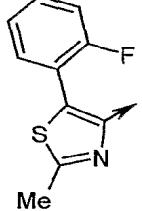
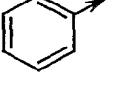
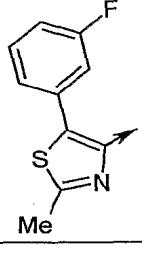
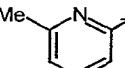
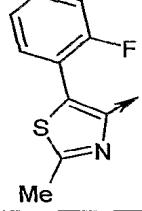
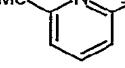
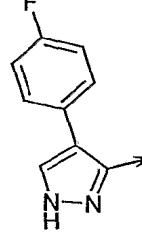
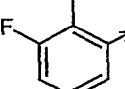
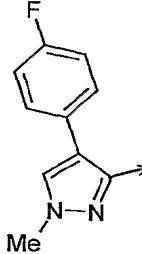
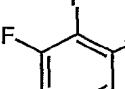
15	D12	1			71	Found 497, 499 (MH ⁺). C ₂₅ H ₂₂ ClFN ₄ O ₂ S. requires 496, 498
16	D14	2			79	Found 497, 499 (MH ⁺). C ₂₅ H ₂₂ ClFN ₄ O ₂ S. requires 496, 498
17	D14	2			7	Found 464, 466 (MH ⁺). C ₂₄ H ₂₂ ClN ₅ O ₃ . requires 463, 465
18	D16	2			62	Found 532, 534, 466 (MH ⁺). C ₂₅ H ₂₁ Cl ₂ FN ₄ O ₂ S. requires 531, 533
19	D19	1			63	Found 481 (MH ⁺). C ₂₅ H ₂₂ F ₂ N ₄ O ₂ S. requires 480
20	D21	1			6	Found 503 (MH ⁺). C ₂₇ H ₂₃ FN ₄ O ₃ S. requires 502

21	D19	1			52	Found 464 (MH^+). $C_{25}H_{23}F_2N_5O_2$. requires 463
22	D19	1			44	Found 465 (MH^+). $C_{24}H_{22}F_2N_6O_2$. requires 464
23	D19	1			50	Found 416 (MH^+). $C_{25}H_{22}FN_3O_2$. requires 415
24	D23	1			69	Found 499 (MH^+). $C_{25}H_{21}F_3N_4O_2S$. requires 498
25	D2	1			54	Found 446 (MH^+). $C_{25}H_{24}FN_5O_2$. requires 445
26	D25	1			56	Found 499 (MH^+). $C_{25}H_{21}F_3N_4O_2S$. requires 498

27	D25	1			50	Found 468 (MH ⁺). C ₂₄ H ₂₀ F ₃ N ₅ O ₂ . requires 467
28	D25	1			44	Found 482 (MH ⁺). C ₂₅ H ₂₂ F ₃ N ₅ O ₂ . requires 481
29	D27	1			69	Found 499 (MH ⁺). C ₂₅ H ₂₁ F ₃ N ₄ O ₂ S. requires 498
30	D27	1			65	Found 485 (MH ⁺). C ₂₄ H ₁₉ F ₃ N ₄ O ₂ S. requires 484
31	D27	1			56	Found 468 (MH ⁺). C ₂₄ H ₂₀ F ₃ N ₅ O ₂ . requires 467
32	D27	1			44	Found 482 (MH ⁺). C ₂₅ H ₂₂ F ₃ N ₅ O ₂ . requires 481

33	D29	2			44	Found 478 (MH ⁺). C ₂₅ H ₂₄ FN ₅ O ₂ S. requires 477
34	D29	2			23	Found 447 (MH ⁺). C ₂₄ H ₂₃ FN ₆ O ₂ . requires 446
35	D29	2			29	Found 461 (MH ⁺). C ₂₅ H ₂₅ FN ₆ O ₂ . requires 460
36	D4	2			77	Found 467 (MH ⁺). C ₂₄ H ₂₀ F ₂ N ₄ O ₂ S. requires 466
37	D31	2			40	Found 453 (MH ⁺). C ₂₃ H ₂₁ FN ₄ O ₃ S. requires 452
38	D31	2			45	Found 422 (MH ⁺). C ₂₂ H ₂₀ FN ₅ O ₃ . requires 421

39	D31	2			50	Found 436 (MH ⁺). C ₂₃ H ₂₂ FN ₅ O ₃ . requires 435
40	D31	2			53	Found 437 (MH ⁺). C ₂₂ H ₂₁ FN ₆ O ₃ . requires 436
41	D4	2			77	Found 467 (MH ⁺). C ₂₄ H ₂₀ F ₂ N ₄ O ₂ S. requires 466
42	D4	1			69	Found 481 (MH ⁺). C ₂₅ H ₂₂ F ₂ N ₄ O ₂ S. requires 480
43	D4	2			85	Found 481 (MH ⁺). C ₂₅ H ₂₂ F ₂ N ₄ O ₂ S. requires 480
44	D2	2			76	Found 449 (MH ⁺). C ₂₄ H ₂₁ FN ₄ O ₂ S. requires 448

45	D2	1			69	Found 463 (MH^+). $\text{C}_{25}\text{H}_{23}\text{FN}_4\text{O}_2\text{S}$. requires 462
46	D2	2			80	Found 463 (MH^+). $\text{C}_{25}\text{H}_{23}\text{FN}_4\text{O}_2\text{S}$. requires 462
47	D29	1			27	Found 478 (MH^+). $\text{C}_{25}\text{H}_{24}\text{FN}_5\text{O}_2\text{S}$. requires 477
48	D29	2			80	Found 478 (MH^+). $\text{C}_{25}\text{H}_{24}\text{FN}_5\text{O}_2\text{S}$. requires 477
49	D23	1			69	Found 468 (MH^+). $\text{C}_{24}\text{H}_{20}\text{F}_3\text{N}_5\text{O}_2$. requires 467
50	D23	1			72	Found 482 (MH^+). $\text{C}_{25}\text{H}_{22}\text{F}_3\text{N}_5\text{O}_2$. requires 481

181	D23	1			64	Found 483 (MH ⁺). C ₂₄ H ₂₁ F ₃ N ₆ O ₂ . requires 482
125	D4	1				Found 448 (MH ⁺). C ₂₅ H ₂₂ FN ₃ O ₂ S. requires 447
126	D4	1				Found 448 (MH ⁺). C ₂₅ H ₂₂ FN ₃ O ₂ S. requires 447
127	D4	1				Found 432 (MH ⁺). C ₂₄ H ₂₂ FN ₅ O ₂ . requires 431
128	D4	1				Found 467 (MH ⁺). C ₂₈ H ₂₃ FN ₄ O ₂ . requires 466
129	D4	1				Found 472 (MH ⁺). C ₂₈ H ₂₆ FN ₃ O ₃ . requires 471
130	D4	1				Found 431 (MH ⁺). C ₂₅ H ₂₃ FN ₄ O ₂ . requires 430
131	D4	1				Found 456 (MH ⁺). C ₂₇ H ₂₂ FN ₃ O ₃ . requires 455
132	D4	1				Found 410 (MH ⁺). C ₂₃ H ₂₄ FN ₃ O ₃ . requires 409

133	D4	1			Found 424 (MH ⁺). C ₂₄ H ₂₆ FN ₃ O ₃ . requires 423
134	D4	1			Found 465 (MH ⁺). C ₂₂ H ₂₀ Cl ₂ FN ₃ O ₃ . requires 464
135	D4	1			Found 446 (MH ⁺). C ₂₆ H ₂₄ FN ₃ O ₃ . requires 445
136	D4	1			Found 463 (MH ⁺). C ₂₆ H ₂₇ FN ₄ O ₃ . requires 462
137	D4	1			Found 449(MH ⁺). C ₂₅ H ₂₅ FN ₄ O ₃ . requires 448
138	D4	1			Found 517(MH ⁺). C ₂₈ H ₂₅ FN ₄ O ₅ . requires 516
139	D4	1			Found 501 (MH ⁺). C ₂₈ H ₂₅ FN ₄ O ₄ . requires 500
140	D4	1			Found 487 (MH ⁺). C ₂₇ H ₂₃ FN ₄ O ₄ . requires 486

141	D4	1				Found 406 (MH ⁺). C ₂₃ H ₂₀ FN ₃ O ₃ . requires 405
142	D4	1				Found 502, 504 (MH ⁺). C ₂₄ H ₂₅ BrFN ₃ O ₃ . requires 501, 503
143	D2	1			85%	Found 460 (MH ⁺). C ₂₆ H ₂₆ FN ₅ O ₂ . requires 459

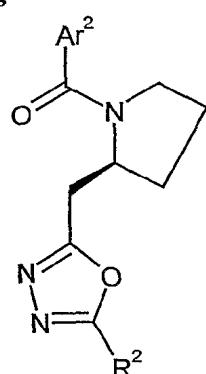
Example 51 1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[*(S*)-2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-pyrrolidin-1-yl]-methanone

5 The title compound (0.01g) was prepared from the amine of description 33 (0.069g) and 2-methyl-5-(4-fluorophenyl)-thiazole-4-carboxylic acid (0.07g) according to the method of example 1.

Mass Spectrum (API): .

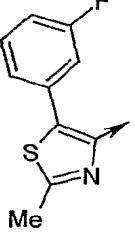
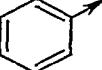
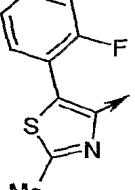
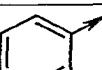
10 The compounds of the examples of Table 2 were prepared by analogous procedures to those used to prepare the compounds of example 51

Table 2: Pyrrolidine Aryl oxadiazoles



15

Example	Amine	Ar ²	R ²	yield	Mass Spectrum
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				%	(Electrospray LC/MS)
52	D33			46	Found 449 (MH ⁺). C ₂₄ H ₂₁ FN ₄ O ₂ S requires 448
53	D33			24	Found 449 (MH ⁺). C ₂₄ H ₂₁ FN ₄ O ₂ S requires 448

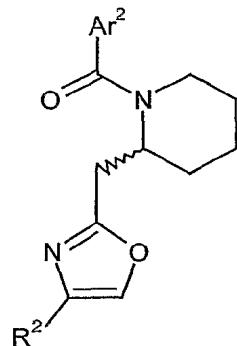
Example 54 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[4-(4-fluoro-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl}-methanone

5 Boron trifluoride diethyl etherate (4 drops) was added to a mixture of the ester of description 36 (0.264g) and acetamide (0.156g) in diethyl ether (2ml). Xylene (1ml) was added and the mixture heated to 140°C for 22h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and washed with water and brine. The organic phase was dried (MgSO₄) and solvent removed at reduced pressure. the residue was column chromatographed (silica gel, 0 → 10 60% ethyl acetate/pentane eluant) to give the title compound (0.145g)
 10 Mass Spectrum (AP⁺): Found 480 (MH⁺). C₂₆H₂₃F₂N₃O₂S requires 479

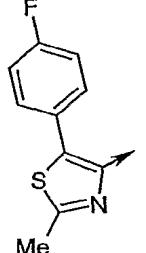
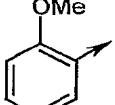
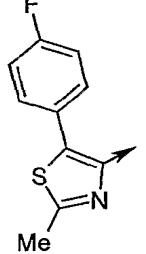
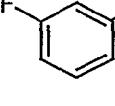
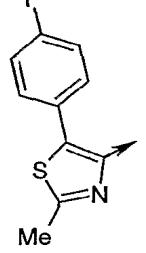
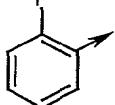
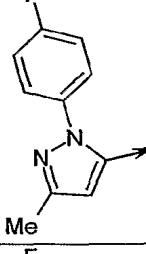
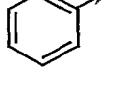
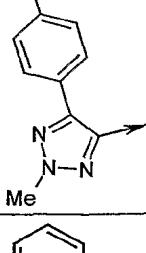
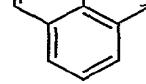
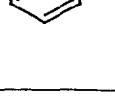
The compounds of the examples of Table 3 were prepared by analogous procedures to those used to prepare the compound of example 54

15

Table 3: Piperidine 2-(4-aryloxazoles)



Example	Ester	Ar ²	R ²	yield	Mass Spectrum
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				%	(Electrospray LC/MS)
55	D37			67	Found 492 (MH ⁺). C ₂₇ H ₂₆ FN ₃ O ₃ S requires 491
56	D38			15	Found 480 (MH ⁺). C ₂₆ H ₂₃ F ₂ N ₃ O ₂ S requires 479
57	D39			46	Found 480 (MH ⁺). C ₂₆ H ₂₃ F ₂ N ₃ O ₂ S requires 479
60	D46			43	Found 445 (MH ⁺). C ₂₆ H ₂₅ FN ₄ O ₂ requires 444
61	D47			16	Found 446 (MH ⁺). C ₂₅ H ₂₄ FN ₅ O ₂ requires 445
62	D48			22	Found 397 (MH ⁺). C ₂₆ H ₂₄ N ₂ O ₂ requires 396

63	D49			39	Found 455, 457 (MH ⁺). C ₂₃ H ₂₃ BrN ₂ O ₃ requires 454, 456
70	D50			85	Found 462 (MH ⁺). C ₂₆ H ₂₄ FN ₃ O ₂ S requires 461
99	D69			46	Found 463 (MH ⁺). C ₂₆ H ₂₄ F ₂ N ₄ O ₂ requires 462
100	D70			30	Found 416 (MH ⁺). C ₂₅ H ₂₂ F ₂ N ₄ O ₂ requires 415
101	D71			30	Found 416 (MH ⁺). C ₂₅ H ₂₂ FN ₃ O ₂ requires 415

Example 58 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(5-methyl-4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone

The title compound (0.28g) was prepared from the ester of description 40 (0.30g) according to the method of example 54.

Mass Spectrum (API⁺): Found 476 (MH⁺). C₂₇H₂₆FN₃O₂S requires 475

Example 59 (RS)-2-(5-(4-Fluorophenyl)-furan-2-ylmethyl)-1-((5-(4-fluorophenyl)-2-methyl-thiazol-4-yl)carbonyl-piperidine

5-(4-Fluorophenyl)-2-methyl-thiazole-4-carbonyl chloride (115 mg, 0.425 mmol) in dichloromethane (1 ml) was added to a solution of (RS)-2-(5-(4-fluorophenyl)-furan-2-ylmethyl)-piperidine (100 mg, 0.386 mmol) and triethylamine (0.16 ml, 1.16 mmol) in dichloromethane (4 ml) and the mixture shaken at ambient temperature for 30 min. The reaction mixture was then washed with saturated aqueous sodium hydrogen carbonate (8 ml) and the organic layer applied

directly onto a pre-packed silica gel column and chromatographed eluting with an ethyl acetate - hexane gradient to give the title compound as a yellow solid (78.0 mg, 42 %).

Mass spectrum (API⁺): 479 (MH⁺): C₂₇H₂₄F₂N₂O₂S requires 478.

5 **Example 64 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(5-phenyl-1H-imidazol-2-ylmethyl)-piperidin-1-yl]-methanone**

The compound of description 50 (0.30g), ammonium acetate (0.38g) and n-butanol (5ml) were combined and boiled for 1h. Solvent was removed at reduced pressure and the residue column chromatographed (silica gel, ethyl acetate then 3% methanol/ethyl acetate) to give the title 10 compound (0.13g).

Mass Spectrum (API⁺): Found 461 (MH⁺). C₂₆H₂₅FN₄OS requires 460.

15 **Example 65 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-ylmethyl]-piperidin-1-yl]-methanone**

The acid of description 35 (0.14g) was dissolved in dichloromethane (10ml) containing 20 dimethylformamide (1 drop). Oxalyl chloride (0.04g) was added and the mixture stirred for 3h. Solvent was removed at reduced pressure, the residue redissolved in dichloromethane (10ml) and added to a solution of 4-fluorobenzamidoxime (0.06g) in pyridine (0.3ml). The mixture was stirred at room temperature for 10 min and boiled for 5h. Solvent was removed at reduced pressure and the residue column chromatographed (silica gel, 20% ether in pentane → dichloromethane eluant) to give the title compound (0.03g).

Mass Spectrum (API⁺): Found 481 (MH⁺). C₂₅H₂₂F₂N₄O₂S requires 480.

25 **Example 66 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[3-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-morpholin-4-yl]-methanone**

The title compound (0.29g) was prepared from the compound of description 52 and 5-phenyltetrazole (0.10g) according to the method of description 1.

Mass Spectrum (API⁺): Found 465 (MH⁺). C₂₄H₂₁FN₄O₃S requires 464.

30 **Example 67 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[3-(4-phenyl-oxazol-2-ylmethyl)-morpholin-4-yl]-methanone**

The title compound (0.131g) was prepared from the compound of description 53 (0.2g) according to the method of example 54.

Mass Spectrum (API⁺): Found 464 (MH⁺). C₂₅H₂₂FN₃O₃S requires 463.

35 **Example 68 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[3-(4-phenyl-1H-imidazol-2-ylmethyl)-morpholin-4-yl]-methanone**

The title compound (0.09g) was prepared from the compound of description 53 (0.20g) according to the method of example 64.

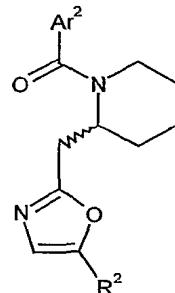
40 Mass Spectrum (API⁺): Found 463 (MH⁺). C₂₅H₂₃FN₄O₂S requires 462.

Example 69 1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-[5-(4-fluoro-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl]-methanone

The title compound (0.11g) was prepared from the amine of description 55 (0.08g) and 2-methyl-5-(4-fluorophenyl)-thiazole-4-carboxylic acid (0.07g) according to the method of description 20. Mass Spectrum (API⁺): Found 480 (MH⁺). C₂₆H₂₃F₂N₃O₂S requires 479.

5 The compounds of the examples of Table 4 were prepared by analogous procedures to those used to prepare the compound of example 69.

Table 4: Piperidine 2-(5-aryloxazoles)



10

Example	Amine	Ar ²	R ²	yield %	Mass Spectrum (Electrospray LC/MS)
71	D55			62	Found 415 (MH ⁺). C ₂₆ H ₂₃ FN ₂ O ₂ requires 414
72	D55			58	Found 425 (MH ⁺). C ₂₄ H ₂₅ FN ₂ O ₄ requires 424
73	D55			60	Found 463 (MH ⁺). C ₂₆ H ₂₄ F ₂ N ₄ O ₂ requires 462
74	D55			58	Found 462 (MH ⁺). C ₂₅ H ₂₃ F ₂ N ₅ O ₂ requires 461

75	D55			63	Found 463 (MH ⁺). C ₂₆ H ₂₄ F ₂ N ₄ O ₂ requires 462
77	D57			56	Found 462 (MH ⁺). C ₂₆ H ₂₄ FN ₃ O ₂ S requires 461
78	D57			44	Found 429 (MH ⁺). C ₂₅ H ₂₄ N ₄ O ₃ requires 428
79	D57			42	Found 473 (MH ⁺). C ₂₂ H ₂₁ IN ₂ O ₂ requires 472

Example 76 (RS)-1-{2-[5-(4-Fluoro-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone

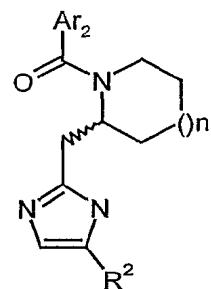
The title compound was prepared from the compound of description 55 (0.07g) and 5-(4-fluorophenyl)-thiazole-4-carboxylic acid chloride (0.06g) according to the method of example 2. Found 466 (MH⁺). C₂₅H₂₁F₂N₃O₂S requires 465.

Example 80 1-{(S)-2-[5-(4-Fluoro-phenyl)-1H-imidazol-2-ylmethyl]-pyrrolidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound (0.09g) was prepared from the amine of description 60 (0.092g) (0.08g) and 2-methyl-5-(4-fluorophenyl)-thiazole-4-carboxylic acid (0.07g) according to the method of description 20. Mass Spectrum (API⁺): Found 465 (MH⁺). C₂₅H₂₂F₂N₄OS requires 464.

The compounds of the examples of Table 5 were prepared by analogous procedures to those used to prepare the compound of example 80.

Table 5: Piperidine and pyrrolidine 2-(4-arylimidazoles)



(S)* against the Example number indicates that the Example was prepared as the (S) enantiomer.

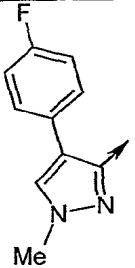
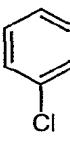
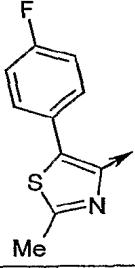
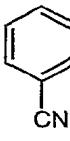
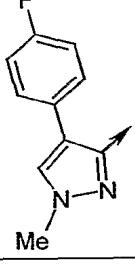
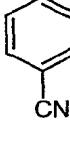
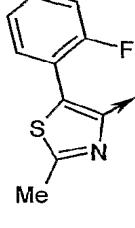
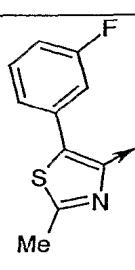
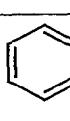
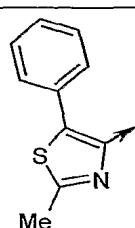
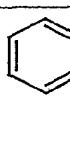
5

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Example	Amine	n	Ar ²	R ²	yield %	Mass Spectrum (Electrospray LC/MS) API ⁺
81 (S)*	60	bond			72	Found 448 (MH ⁺). C ₂₅ H ₂₃ F ₂ N ₅ O S requires 447
82 (S)*	60	bond			75	Found 434 (MH ⁺). C ₂₄ H ₂₁ F ₂ N ₅ O S requires 433
83	63	1			42	Found 479 (MH ⁺). C ₂₆ H ₂₄ F ₂ N ₄ O S requires 478

84	63	1			59	Found 462 (MH ⁺). C ₂₆ H ₂₅ F ₂ N ₅ O requires 461
85	63	1			45	Found 448 (MH ⁺). C ₂₅ H ₂₃ F ₂ N ₅ O requires 447
86	63	1			72	Found 395 (MH ⁺). C ₂₂ H ₂₃ FN ₄ O ₂ requires 394
87	63	1			28	Found 415 (MH ⁺). C ₂₅ H ₂₃ FN ₄ O requires 414
88	63	1			24	Found 416 (MH ⁺). C ₂₄ H ₂₂ FN ₅ O requires 415
89	63	1				Found 519 (MH ⁺). C ₂₉ H ₃₂ F ₂ N ₆ O requires 518
90	63	1				Found 495 (MH ⁺). C ₂₆ H ₂₄ F ₂ N ₄ O ₂ S requires 494

91	63	1					Found 463 (MH ⁺). C ₂₅ H ₂₄ F ₂ N ₆ O requires 462
92	63	1					Found 446 (MH ⁺). C ₂₅ H ₂₄ FN ₅ O ₂ requires 445
104	74	1			18		Found 477 (MH ⁺). C ₂₆ H ₂₅ FN ₄ O ₂ S requires 476
108	84	1			53		Found 491 (MH ⁺). C ₂₇ H ₂₇ FN ₄ O ₂ S requires 490. Isolated as the HCl salt
109	84	1			35		Found 474 (MH ⁺). C ₂₇ H ₂₈ FN ₅ O ₂ requires 473 Isolated as the HCl salt
110	87	1			60		Found 496(MH ⁺). C ₂₆ H ₂₄ ³⁷ ClFN 4OS requires 495 Isolated as the HCl salt

111	87	1			55	Found 480 (MH ⁺). C ₂₆ H ₂₅ ³⁷ ClFN 5O requires 479 Isolated as the HCl salt
112	90	1			25	Found 486 (MH ⁺). C ₂₇ H ₂₄ FN ₅ OS requires 485 Isolated as the HCl salt
113	90	1			25	Found 469 (MH ⁺). C ₂₇ H ₂₅ FN ₆ O requires 468 Isolated as the HCl salt
114	74	1				Mass Spectrum Found 461 (MH ⁺). C ₂₆ H ₂₅ FN ₄ OS requires 460.
115	74	1				Mass Spectrum Found 461 (MH ⁺). C ₂₆ H ₂₅ FN ₄ OS requires 460.
116	74	1				Mass Spectrum Found 433 (MH ⁺). C ₂₆ H ₂₆ N ₄ OS requires 432.

117	74	1				Mass Spectrum Found 544 (MH ⁺). C ₃₁ H ₃₇ N ₅ O ₂ S requires 543.
118	74	1				Mass Spectrum Found 558 (MH ⁺). C ₃₂ H ₃₉ N ₅ O ₂ S requires 557.
119	74	1				Mass Spectrum Found 530 (MH ⁺). C ₃₀ H ₃₅ N ₅ O ₂ S requires 529.
159	106	1			34%	Mass Spectrum Found 497 (MH ⁺). C ₂₆ H ₂₃ F ₃ N ₄ O S requires 496.
160	107	1			34%	Mass Spectrum Found 479 (MH ⁺). C ₂₆ H ₂₄ F ₂ N ₄ O S requires 478.

Example 93 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[5-(2-methoxyphenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl}-methanone

The title compound (0.17g) was prepared from the compound of description 37 (0.50g) according to the method of description 59.

Found 491 (MH⁺). C₂₇H₂₇FN₄O₂S requires 490.

5 **Example 94 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[5-(2-fluorophenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl}-methanone**

The title compound (0.035g) was prepared from the compound of description 39 (0.21g) according to the method of description 59.

Found 479 (MH⁺). C₂₆H₂₄F₂N₄OS requires 478.

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Example 95 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[5-(2-bromophenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl}-methanone

The title compound (0.18g) was prepared from the compound of description 64 (0.50g) according to the method of description 59.

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Found 539, 541 (MH⁺) C₂₆H₂₄BrFN₄OS requires 538, 540

Example 96 (RS)-2-[2-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-3H-imidazol-4-yl]-benzonitrile

The compound of example 95 (0.11g) and copper(I) cyanide (0.03g) were combined in N-

20

methylpyrrolidinone (5ml) and the mixture boiled for 6h. After cooling to room temperature the reaction mixture was stood overnight, diluted with ethyl acetate, passed through silica gel eluting with ethyl acetate/water. The organic phase was separated washed with water dried (MgSO₄) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 20 → 100% ethyl acetate/pentane), the appropriate fractions combined and solvent removed at reduced pressure to give the title compound (0.03g) as a gum

25

Found 485 (MH⁺) C₂₇H₂₄FN₅OS requires 486.

Example 97 (RS)-1-{2-[4-Bromo-5-(4-fluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

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The title compound (0.17g) was prepared by treating the compound of description 68 (0.27g), 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.19g), 1-hydroxybenzotriazole (0.05g) and diisopropylethylamine ((0.35ml) in dimethylformamide (5ml) with EDC.HCl. The mixture was stirred for 20h, diluted with diethyl ether and washed with sodium carbonate and water (x3), dried (MgSO₄) and solvent removed at reduced pressure. The residue was column

35

chromatographed (silica gel, 0 → 2% methanol/dichloromethane), the appropriate fractions combined and solvent removed at reduced pressure to give the title compound (0.17g) as a gum
Found 557, 559 (MH⁺) C₂₆H₂₃BrF₂N₄OS requires 556, 558.

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Example 98 (RS)-5-(4-Fluoro-phenyl)-2-(1-{1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-3H-imidazole-4-carbonitrile The title compound (0.038g) was prepared from the compound of example 97 (0.22g) according to the method of example 96. Found 504 (MH⁺) C₂₇H₂₃F₂N₅OS requires 503.

Example 102 (RS)-1-(2-Ethoxy-phenyl)-1-[2-(4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone

The title compound (0.065g) was prepared from the compound of description 77 (0.060g) and 2-ethoxybenzoic acid (0.042g) according to the method of example 1

5 Found 391 (MH⁺) C₂₄H₂₆N₂O₃ requires 390.

Example 103 (RS)-1-[5-(4-Fluoro-phenyl)-2-hydroxymethyl-thiazol-4-yl]-1-[2-(4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone

The title compound (0.055g) was prepared from the compound of description 77 (0.15g) and 5-

10 (4-fluoro-phenyl)-2-hydroxymethyl-thiazole-4-carboxylic acid (0.042g) according to the method of example 97

Found 478 (MH⁺) C₂₆H₂₄FN₃O₃S requires 477.

Example 105 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[5-(4-fluoro-phenyl)-4H-[1,2,4]triazol-3-ylmethyl]-piperidin-1-yl}-methanone

A solution of the compound of description 78 (0.20g) and 4-fluorobenzamidine (0.11g) in ethanol (5ml) was treated with a 25% sodium methoxide in methanol solution (0.24ml) and the mixture refluxed for 60h. Solvent was removed at reduced pressure, the residue partitioned between dichloromethane/water, the organic phase separated, dried (MgSO₄) and solvent removed at

20 reduced pressure to give the title compound (0.04g)

Found 480 (MH⁺) C₂₅H₂₃F₂N₅OS requires 479.

Example 106 (RS)- 1-{2-[5-(4-Fluoro-phenyl)-4H-[1,2,4]triazol-3-ylmethyl]-piperidin-1-yl}-1-isoquinolin-3-yl-methanone

25 The title compound (0.006g) was prepared from the compound of description 81 (0.08g) and isoquinoline-3-carboxylic acid (0.06g) according to the method of description 20.

Found 416 (MH⁺) C₂₄H₂₂FN₅O requires 415.

Example 107 (RS)-1-{2-[3-(3-Dimethylamino-propoxy)-phenyl]-thiophen-3-yl}-1-[2-[4-(4-fluoro-phenyl)-1H-imidazol-2-ylmethyl]-piperidin-1-yl}-methanone

The title compound (0.006g) was prepared from the compound of description 63 (0.071g) and 2-[3-(3-Dimethylamino-propoxy)-phenyl]-thiophene-3-carbonyl chloride

Found 547 (MH⁺) C₃₁H₃₅FN₄O₂S requires 546.

35 Example 120 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[5-(4-fluoro-phenyl)-tetrazol-2-ylmethyl]-piperidin-1-yl}-methanone

The title compound (0.14g) was prepared from the compound of description 92 (0.09g) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.08g) according to the method of Description 20.

40 Found 481(MH⁺) C₂₄H₂₂F₂N₆OS requires 480.

Example 121 (RS)-1-{2-[5-(4-Fluoro-phenyl)-tetrazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-thiazol-4-yl]-methanone

The title compound (0.13g) was prepared from the compound of description 92 (0.09g) and 5-(4-fluoro-phenyl)-thiazole-4-carboxylic acid (0.074g) according to the method of Description 20. Found 467(MH⁺) C₂₃H₂₀F₂N₆OS requires 466.

5 **Example 122 (RS)-1-[4-(4-Fluoro-phenyl)-1H-pyrazol-3-yl]-1-[2-[5-(4-fluoro-phenyl)-tetrazol-2-ylmethyl]-piperidin-1-yl]-methanone**

The title compound (0.10g) was prepared from the compound of description 92 (0.09g) and 4-(4-Fluoro-phenyl)-1H-pyrazole-3-carboxylic acid (0.070g) according to the method of Description 20.

10 Found 450 (MH⁺) C₂₃H₂₁F₂N₇O requires 449.

Example 123 (RS)-1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-[2-[5-(4-fluoro-phenyl)-tetrazol-2-ylmethyl]-piperidin-1-yl]-methanone

The title compound (0.13g) was prepared from the compound of description 92 (0.09g) and 4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazole-3-carboxylic acid (0.070g) according to the method of Description 20.

Found 464(MH⁺) C₂₄H₂₃F₂N₇O requires 463.

20 **Example 124 (RS)-1-[4-(4-Fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-1-[2-[5-(4-fluoro-phenyl)-tetrazol-2-ylmethyl]-piperidin-1-yl]-methanone**

The title compound (0.03g) was prepared from the compound of description 92 (0.09g) and 4-(4-fluoro-phenyl)-2-methyl-2H-pyrazole-3-carboxylic acid (0.070g) according to the method of Description 20.

Found 464 (MH⁺) C₂₄H₂₃F₂N₇O requires 463.

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Example 144 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(4-phenyl-imidazol-1-ylmethyl)-piperidin-1-yl]-methanone

The title compound (0.065g) was prepared from the compound of description 94 (0.07g) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.069g) according to the method of

30 Description 20.

Found 461 (MH⁺) C₂₆H₂₅FN₄OS requires 460.

Example 145 (RS)-1-[5-(4-Fluoro-phenyl)-thiazol-4-yl]-1-[2-(4-phenyl-imidazol-1-ylmethyl)-piperidin-1-yl]-methanone

35 The title compound (0.10g) was prepared from the compound of description 94 (0.07g) and 5-(4-Fluoro-phenyl)-thiazole-4-carboxylic acid (0.065g) according to the method of Description 20.

Found 447(MH⁺) C₂₅H₂₃FN₄OS requires 446.

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Example 146 (RS)-1-[4-(4-Fluoro-phenyl)-1-methyl-1H-pyrazol-3-yl]-1-[2-(4-phenyl-imidazol-1-ylmethyl)-piperidin-1-yl]-methanone

The title compound (0.135g) was prepared from the compound of description 94 (0.07g) and 4-(4-fluoro-phenyl)-1-methyl-1H-pyrazole-3-carboxylic acid (0.064g) according to the method of Description 20.

Found 444 (MH^+) $\text{C}_{26}\text{H}_{26}\text{FN}_5\text{O}$ requires 443.

Example 147 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[3-(4-fluoro-phenyl)-pyrazol-1-ylmethyl]-piperidin-1-yl}-methanone

5 The title compound (0.10g) was prepared from the compound of description 96 (0.086g) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.075g) according to the method of Description 20.

Found 479 (MH^+) $\text{C}_{26}\text{H}_{24}\text{F}_2\text{N}_4\text{OS}$ requires 478.

10 **Example 148 (RS)-1-(5-Bromo-2-methoxy-phenyl)-1-{2-[3-(4-fluoro-phenyl)-pyrazol-1-ylmethyl]-piperidin-1-yl}-methanone**

The title compound (0.125g) was prepared from the compound of description 96 (0.086g) and 5-bromo-2-methoxybenzoic acid (0.08g) according to the method of Description 20.

15 **Example 149 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-2H-[1,2,3]triazol-4-yl]-1-{2-[3-(4-fluoro-phenyl)-pyrazol-1-ylmethyl]-piperidin-1-yl}-methanone**

The title compound (0.09g) was prepared from the compound of description 96 (0.086g) and 5-(4-fluoro-phenyl)-2-methyl-2H-[1,2,3]triazole-4-carboxylic acid (0.078g) according to the method of Description 20.

20 Found (MH^+) 463 $\text{C}_{25}\text{H}_{24}\text{F}_2\text{N}_6\text{O}$ requires 462.

Example 150 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-oxazol-4-yl]-1-{2-[3-(4-fluoro-phenyl)-pyrazol-1-ylmethyl]-piperidin-1-yl}-methanone

25 The title compound (0.11g) was prepared from the compound of description 96 (0.086g) and 5-(4-fluoro-phenyl)-2-methyl-oxazole-4-carboxylic acid (0.078g) according to the method of Description 20.

Found 463 (MH^+) $\text{C}_{26}\text{H}_{24}\text{F}_2\text{N}_4\text{O}_2$ requires 462.

30 **Example 151 1-{2-[3-(4-Fluoro-phenyl)-pyrazol-1-ylmethyl]-piperidin-1-yl}-1-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone**

The title compound (0.05g) was prepared from the compound of description 96 (0.086g) and 2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-benzoic acid (0.070g) according to the method of Description 20.

Found 446 (MH^+) $\text{C}_{25}\text{H}_{24}\text{FN}_5\text{O}_2$ requires 445.

35 **Example 152 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(4-phenyl-thiazol-2-ylmethyl)-piperidin-1-yl]-methanone**

The title compound (0.133g) was prepared from the compound of description 99 (0.184g) according to the method of description 20.

Found 478 (MH^+) $\text{C}_{26}\text{H}_{24}\text{FN}_3\text{OS}_2$ requires 477.

40 **Example 153 (R)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[3-(4-phenyl-oxazol-2-ylmethyl)-morpholin-4-yl]-methanone and (S)-(R)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[3-(4-phenyl-oxazol-2-ylmethyl)-morpholin-4-yl]-methanone**

The title compounds were isolated by chiral HPLC on a Chiralcel OD; 250 mm x 19 mm i.d.; 10 micron particle size column, with a mobile phase of n-Hexane, Ethanol (80:20 v/v) with a flow rate of 17ml/min-1, a runtime of 20min with detection by UV absorbance at 215nM. The racemic compound of example 67 was injected in ethanol (2ml) at 4mg/ml. The two enantiomers

5 were isolated as the faster and slower running components with ee's of 99.4% and 96.6%. Faster running component Mass Spectrum (API⁺): Found 464 (MH⁺). C₂₅H₂₂FN₃O₃S requires 463.

Slower running component Mass Spectrum (API⁺): Found 464 (MH⁺). C₂₅H₂₂FN₃O₃S requires 463.

10 **Example 154 (RS)-1-[2-[5-(2,5-Dimethyl-2H-pyrazol-3-yl)-[1,3,4]oxadiazol-2-ylmethyl]-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone**

The compound of description 101 (0.35g) and polyphosphoric acid (0.70g) were combined and warmed at 140°C for 4h. The reaction was cooled to room temperature, potassium carbonate and 15 iced water added. the basic solution was extracted with dichloromethane (x2), the combined organic phase washed with water, dried and solvent removed at reduced pressure. The residue was column chromatographed (silica gel; 20% ethyl acetate in pentane eluant) to give the title compound (0.073g)

Mass Spectrum (API⁺): Found 481 (MH⁺). C₂₄H₂₅FN₆O₂S requires 480.

20 **Example 155 (RS)-1-[2-(4,5-Diphenyl-1H-imidazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone**

The title compound (0.34g) was prepared from the compound of description 102 (0.53g) according to the method of example 64.

25 Mass Spectrum (API⁺): Found 537 (MH⁺). C₃₂H₂₉FN₄OS requires 536.

Example 156 (RS)-1-[2-[4-(4-Fluoro-phenyl)-1-methyl-1H-imidazol-2-ylmethyl]-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The compound of example 83 (0.25g) was added to sodium hydride (60% in oil, 0.042g) in 30 dimethylformamide (5ml) and stirred until gas evolution had ceased. Iodomethane 0.163g) was added, stirring continued for 16h, diluted carefully with water and extracted with ethyl acetate (x4). The combined organic phase was washed with water and brine, dried (MgSO₄) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 50% ethyl acetate:pentane eluant) to give after combining appropriate fractions the title compound (0.06g).

35 Mass Spectrum (API⁺): Found 493 (MH⁺). C₂₇H₂₆F₂N₄OS requires 492.

Example 157 (RS)-1-[2-(5-Benzofuran-2-yl-[1,3,4]oxadiazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(3-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound (0.038g) was prepared from the compound of description 104 and 5-(3-40 Fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.068g) according to the method of description 20.

Mass Spectrum (API⁺): Found 503 (MH⁺). C₂₇H₂₃FN₄O₃S requires 502.

Example 158 (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(4-pyridin-2-yl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone

The compound of description 105 (0.56g) and 2-bromo-1-pyridin-2-yl-ethanone (0.44g) were combined in dichloromethane (2ml). The mixture was heated to 100°C until the dichloromethane had evaporated and then heating continued at 140°C for 6h. The reaction was cooled to room temperature, and the residue dissolved in sodium hydroxide/dichloromethane, the organic phase separated, dried, solvent removed at reduced pressure and the residue column chromatographed (silica gel; 0 → 8% methanol/dichloromethane) to give after combining the appropriate fractions the title compound (0.05g)

10 Mass Spectrum (API⁺): Found 463 (MH⁺). C₂₅H₂₃FN₄O₂S requires 462.

Example 161. (RS)-1-[5-(4-Fluorophenyl)-2-methylthiazol-4-yl]-1-{2-[5-(4-fluorophenyl)-1H-pyrazol-3-ylmethyl]-piperidin-1-yl}-methanone

15 The compound of description 108 (0.430g) was dissolved in ethanol (20ml) and stirred at room temperature for 16 hours with hydrazine hydrate (0.087ml). The solution was then evaporated at reduced pressure and chromatographed over silica gel, eluting with a gradient of 0 to 10% [9:1 methanol/conc. ammonia solution] in dichloromethane. The title compound was obtained as a white foam (0.034g), mass spectrum (API⁺) 479 [MH⁺], (API) 477 [(M-H)] C₂₆H₂₄F₂N₄OS requires 478

20 **Example 162. (RS)-1-{2-[4-(4-Fluorophenyl)-1H-imidazol-2-ylmethyl]-piperazin-1-yl}-1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]-methanone**

25 3-[4-(4-Fluorophenyl)-1H-imidazol-2-ylmethyl]-4-{1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]-methanoyl}-piperazine-1-carboxylic acid tert-butyl ester description 112 (0.130g) was dissolved in TFA and stirred under argon at room temperature for 3 hours. The TFA was evaporated and the residue chromatographed over silica gel, eluting with a gradient of 0 to 10% [9:1 methanol/conc. ammonia solution] in dichloromethane. The title compound was obtained as a white foam (0.095g), mass spectrum (API⁺) 480 [MH⁺], C₂₅H₂₃F₂N₅OS requires 479.

30 **Example 163. 1-[5-(4-Fluorophenyl)-2-methyl-thiazol-4-yl]-1-{2-[4-(4-fluorophenyl)-oxazol-2-ylmethyl]-piperazin-1-yl}-methanone**

35 4-{1-[5-(4-Fluorophenyl)-2-methyl-thiazol-4-yl]-methanoyl}-3-[4-(4-fluoro-phenyl)-oxazol-2-ylmethyl]-piperazine-1-carboxylic acid tert-butyl ester (0.130g) was dissolved in trifluoroacetic acid (10ml) and stirred at room temperature for 2 hours. The reaction mixture was then evaporated to dryness at reduced pressure and the residue was chromatographed over silica gel. Elution with a gradient of 0 to 10% [9:1 methanol/conc. ammonia solution] in dichloromethane provided the title compound as a pale yellow gum (0.013g), mass spectrum (API⁺) 481 [MH⁺], C₂₅H₂₂F₂N₄O₂S requires 480.

40 **Example 164. (RS)-1-[3-(5-Bromo-4-phenyl-oxazol-2-ylmethyl)-morpholin-4-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone**

The compound of example 67 (0.152g) was dissolved in carbon tetrachloride (10ml) and was then treated with N-bromosuccinimide (0.058g) and stirred under argon at room temperature for 24h. A further quantity of N-bromosuccinimide (0.006g) was added and the mixture stirred for a further 1h. The mixture was filtered through a cotton wool plug and the filtrate was evaporated to dryness under reduced pressure. The residue was column chromatographed (silica gel, 0 → 40% ethyl acetate-pentane) to give the title compound (0.117g).

5 Mass Spectrum (API⁺ LC/MS): Found 542, 544. $C_{25}H_{21}BrFN_3O_3S$ requires 541,543.

Example 165. (RS)-1-[2-(5-Chloro-4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The oxazole of example 70 (0.06g) in carbon tetrachloride (10ml) was treated with N-chlorosuccinimide (0.018g) and stirred at room temperature, under argon, for 6h. A further quantity of N-chlorosuccinimide (0.009g) was added and the mixture heated at 80°C, under argon for 16h. The solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was dried (magnesium sulfate) and the solvent removed under reduced pressure. The residue was column chromatographed (silica gel; 0 → 40% ethyl acetate-pentane) to afford the title compound (0.024g).

10 Mass Spectrum (Electrospray LC/MS): 496,498 (MH^+). $C_{26}H_{23}ClFN_3O_2S$ requires 495,497.

Example 166. 1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-(5-phenyl-4H-[1,2,4]triazol-3-ylmethyl)-pyrrolidin-1-yl]-methanone

The title compound (0.077g) was prepared from the amine of description 117 (0.072g) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.075g) according to the method of example 1.

15 Mass Spectrum (API⁺ LC/MS): 448 (MH^+). $C_{24}H_{22}FN_5OS$ requires 447.

Example 167. (RS)-1-[2-(5-Bromo-4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound (0.412g) was prepared by treating the compound of example 70 with N-bromosuccinimide (0.190g) according to the method of example 164.

20 Mass Spectrum (Electrospray LC/MS): 540, 542 (MH^+). $C_{26}H_{23}BrFN_3O_2S$ requires 539, 541.

Example 168. (RS)-1-(2-Methyl-5-phenyl-thiazol-4-yl)-1-[2-(4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone

25 The title compound (0.165g) was prepared from the amine of description 77 (0.116g) and 2-Methyl-5-phenyl-thiazole-4-carboxylic acid (0.105g) according to the method of example 1.

Mass Spectrum (Electrospray LC/MS): 444 (MH^+). $C_{26}H_{25}N_3O_2S$ requires 443.

Example 169. (RS)-1-[1-(2-Dimethylamino-ethyl)-4-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-1-[2-(4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone

30 The title compound (0.169g) was prepared from the amine of description 77 (0.116g) and 1-(2-Dimethylamino-ethyl)-4-(4-fluoro-phenyl)-1H-pyrazole-3-carboxylic acid (0.132g) according to the method of example 1.

Mass Spectrum (Electrospray LC/MS): 502 (MH^+). $C_{29}H_{32}FN_5O_2$ requires 501.

Example 170. (RS)-2-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-piperidin-2-ylmethyl)-4-phenyl-oxazole-5-carbonitrile

5 The title compound (50mg) was prepared by treating the compound of example 167 (0.410g) with copper(I)cyanide (0.103g) according to the method of example 96. Following column chromatography, further purification by HPLC was required (Supercosil ABZ+, 5-95% acetonitrile containing 0.1% trifluoroacetic acid-water containing 0.1% trifluoroacetic acid). Mass Spectrum (Electrospray LC/MS): 487 (MH^+). $C_{27}H_{23}FN_4O_2S$ requires 486.

10 **Example 171. (RS)-1-[2-(5-Bromo-4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-1-(2-methyl-5-phenyl-thiazol-4-yl)-methanone**

The title compound (0.075g) was prepared by treating the compound of example 168 (0.093g) with *N*-bromosuccinimide (0.037g) according to the method of example 164.

15 Mass Spectrum (Electrospray LC/MS): 522,524 (MH^+). $C_{26}H_{24}BrFN_3O_2S$ requires 521,523.

Example 172. 1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-[(S)-2-(4-phenyl-oxazol-2-ylmethyl)-pyrrolidin-1-yl]-methanone

20 The title compound (0.103g) was prepared from the amine of description 120 (0.061g) and 5-(4-fluoro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.064g) according to the method of example 1.

Mass Spectrum (Electrospray LC/MS): 448 (MH^+). $C_{25}H_{22}FN_3O_2S$ requires 447.

Example 173. 1-[(S)-2-(5-Bromo-4-phenyl-oxazol-2-ylmethyl)-pyrrolidin-1-yl]-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

25 The title compound (0.066g) was prepared by treating the compound of example 172 (0.075g) with *N*-bromosuccinimide (0.030g) according to the method of example 164.

Mass Spectrum (Electrospray LC/MS): 526,528 (MH^+). $C_{25}H_{21}BrFN_3O_2S$ requires 525,527.

30 **Example 174. (RS)-1-[5-(4-Chloro-phenyl)-2-methyl-thiazol-4-yl]-1-[2-(4-phenyl-oxazol-2-ylmethyl)-piperidin-1-yl]-methanone**

The title compound (0.106g) was prepared from the amine of description 77 (0.072g) and 5-(4-chloro-phenyl)-2-methyl-thiazole-4-carboxylic acid (0.076g) according to the method of example 1. Mass Spectrum (API⁺ LC/MS): 478,480 (MH^+). $C_{26}H_{24}ClN_3O_2S$ requires 477, 479.

35 **Example 175. (RS)-1-[4-(4-Fluoro-phenyl)-1-methyl-1*H*- pyrazol-3-yl]-1-[2-(4-phenyl-thiazol-2-ylmethyl)-piperidin-1-yl]-methanone**

The title compound (0.022g) was prepared from the compound of description 99 (0.060g) and 4-(4-Fluoro-phenyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid (0.044g) according to the method of example 1.

40 Mass Spectrum (Electrospray LC/MS): Found 461(MH^+). $C_{26}H_{25}FN_4OS$ requires 460.

Example 176. (RS)-1-{2-[4-(2-Bromo-phenyl)-oxazol-2-ylmethyl]-piperidin-1-yl}-1-[5-(4-fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanone

The title compound (0.50g) was prepared from the compound of description 121 (2.00g), acetamide (1.05g) and boron trifluoride.diethyl etherate (0.7ml) in xylene according to the method of example

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54.

Mass Spectrum (Electrospray LC/MS): Found 540,542 (MH^+). $C_{26}H_{23}BrFN_3O_2S$ requires 539,541.

Example 177. (RS)-2-[2-(1-{1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-methanoyl}-**piperidin-2-ylmethyl)-oxazol-4-yl]-benzonitrile**

A mixture of the bromide (0.240g) of example 176, Cu(I)CN (0.060g) and N-Methyl pyrrolidinone (5 ml) was heated at 180 °C for 16h. The cooled reaction mixture was diluted with ethyl acetate and passed through kieselguhr, washing with ethyl acetate. The filtrate was washed with water, dried (sodium sulfate) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 20-50% ethyl acetate-pentane) to give the title compound as a pale yellow gum (0.101g)

15

Mass Spectrum (API⁺ LC/MS): Found 487 (MH^+). $C_{27}H_{23}FN_4O_2S$ requires 486.

Example 178. (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[4-(2-fluoro-phenyl)-thiazol-2-ylmethyl]-piperidin-1-yl}-methanone

The title compound (0.235g) was prepared as a solid from the amine of description 122 (0.330g) and 2-methyl-5-(4-fluoro-phenyl)-thiazole-4-carboxylic acid (0.283g) according to the method of example 1.

Mass Spectrum (Electrospray LC/MS): Found 496 (MH^+). $C_{26}H_{23}F_2N_3OS_2$ requires 495.

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Example 179. (RS)-1-[5-(4-Fluoro-phenyl)-2-methyl-thiazol-4-yl]-1-{2-[4-(3-fluoro-phenyl)-thiazol-2-ylmethyl]-piperidin-1-yl}-methanone

The title compound (0.047g) was prepared as a solid from the amine of description 123 (0.100g) and 2-methyl-5-(4-fluoro-phenyl)-thiazole-4-carboxylic acid (0.086g) according to the method of example 1.

30

Mass Spectrum (Electrospray LC/MS): Found 496 (MH^+). $C_{26}H_{23}F_2N_3OS_2$ requires 495.

Example 180. (RS)-1-{2-[4-(3-Fluoro-phenyl)-thiazol-2-ylmethyl]-piperidin-1-yl}-1-(2-methyl-5-phenyl-thiazol-4-yl)-methanone

The title compound (0.031g) was prepared as a solid from the amine of description 123 (0.100g) and 2-methyl-5-phenyl-thiazole-4-carboxylic acid (0.079g) according to the method of example 1.

Mass Spectrum (Electrospray LC/MS): Found 478 (MH^+). $C_{26}H_{24}FN_3OS_2$ requires 477.

It is understood that the present invention covers all combinations of particular and preferred groups described herein above.

40

Determination of Orexin-1 Receptor Antagonist Activity

The orexin-1 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

5 CHO-DG44 cells expressing the human orexin-1 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 µl/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 µg/well of poly-L-lysine from SIGMA. The seeded plates were
10 incubated overnight at 37C in 5% CO₂.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC50 values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM CaCl₂, 1.2 mM MgCl₂ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC50 values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 3.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 µl of cell medium containing probenecid (Sigma) and Fluo3AM 20 (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 µM, respectively. The 96-well plates were incubated for 60 min at 37C in 5% CO₂. The loading solution containing dye was then aspirated and cells were washed with 4x150 µl Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 µl. Antagonist or buffer (25 µl) was 25 added (Quadra) the cell plates gently shaken and incubated at 37C in 5% CO₂ for 30 minutes. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 30 20 seconds (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, *TiPS*, 1995, 16, 413-417) to generate a concentration effect value. Antagonist Kb values were calculated 35 using the equation:

$$Kb = IC50 / (1 + ([3] / EC50))$$

where EC50 was the potency of human orexin-A determined in the assay (in nM terms) and IC50 is expressed in molar terms.

Compounds of Examples tested according to this method had pKb values in the range 6.7 40 - 9.5 at the human cloned orexin-1 receptor.

The orexin-2 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

CHO-DG44 cells expressing the human orexin-2 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 μ l/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 μ g/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37C in 5% CO₂.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC50 values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM CaCl₂, 1.2 mM MgCl₂ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC50 values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 10.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 μ l of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 μ M, respectively. The 96-well plates were incubated for 60 min at 37C in 5% CO₂. The loading solution containing dye was then aspirated and cells were washed with 4x150 μ l Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 μ l. Antagonist or buffer (25 μ l) was added (Quadra) to the cell plates gently shaken and incubated at 37C in 5% CO₂ for 30 min. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 20 sec (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, *TiPS*, 1995, **16**, 413-417) to generate a concentration effect value. Antagonist Kb values were calculated using the equation:

$$Kb = IC50 / (1 + ([3] / EC50))$$

where EC50 was the potency of human orexin-A determined in the assay (in nM terms) and IC50 is expressed in molar terms.

Compounds of Examples tested according to this method had pKb values in the range <6.3 – 8.2 at the human cloned orexin-2 receptor.

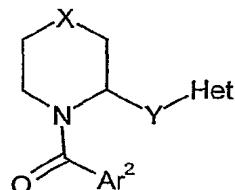
The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without

limitation the following claims:

CLAIMS

1. A compound of formula (I):

5



(I)

wherein:

X represents a bond, oxygen, NR³ or a group (CH₂)_n, wherein n represents 1, 2 or 3,

10 Y represents CH₂, CO, CHO_H, or -CH₂CH(OH)-;

Het is an optionally substituted 5- or 6-membered monocyclic heteroaryl group containing up to 4 heteroatoms selected from N, O and S, substituted by R²;

15 Ar² represents an optionally substituted phenyl or a 5- or 6-membered heteroaryl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heteroaryl group is substituted by R¹ and further optional substituents; or Ar² represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic group containing up to 3 heteroatoms selected from N, O and S;

20 R¹ represents hydrogen, an optionally substituted (C₁₋₄)alkoxy, halo, cyano, optionally substituted (C₁₋₆)alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocycl group containing up to 4 heteroatoms selected from N, O and S;

R² is an optionally substituted aryl or an optionally substituted mono or bicyclic heteroaryl group containing up to 3 heteroatoms selected from N, O and S;

R³ is selected from hydrogen or (C₁₋₄)alkyl;
or a pharmaceutically acceptable salt thereof.

25

2. A compound according to claim 1 wherein X is a bond, oxygen or (CH₂)_n where n is 1 or 2.

30 3. A compound according to claim 1 or 2 wherein Ar² represents optionally substituted phenyl, pyridinyl, thiazolyl, pyrazolyl, pyridazyl, thienyl, benzofuranyl, naphthyl or triazolyl.

4. A compound according to any one of claims 1 to 3 wherein R¹ represents an optionally substituted phenyl, pyridinyl, pyrazolyl, pyrimidazyl, or oxadiazolyl group.

35 5. A compound according to any one of claims 1 to 4 wherein Het is oxazolyl, imidazolyl, thiazolyl, triazolyl, oxadiazolyl, pyrazolyl, furanyl and tetrazolyl.

6. A compound according to any one of claims 1 to 5 wherein Y is CH₂.

7. A compound of formula (I) as claimed in Claim 1 selected from Examples 1 to 130 and 132 to 181, or a pharmaceutically acceptable salt of thereof.

8. (RS)-1-dibenzofuran-4-yl-1-{2-[5-(3-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-5-piperidin-1-yl}-methanone or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, or the compound as claimed in claim 8 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

10

10. A method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, or the compound as claimed in claim 8 or a pharmaceutically acceptable salt thereof.

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